Journal of Medical & Radiation Oncology

Volume II, Issue 1 (July 2022)

Supported by

STOP CANCER

aMEcRO

Crossref Cited-by

Journal of Medical and Radiation Oncology is available online:
www.jmedradonc.org

Casa Cărții de Știință
Cluj-Napoca, 2022

Aims and scope

Journal of Medical & Radiation Oncology (JMRO) publishes manuscripts in the field of Clinical Oncology and connected specialties: Radiology, Nuclear Medicine, Oncological surgery, Pathology, Basic science, Molecular biology, Genetics, Epidemiology, Psycho-oncology/psychiatry, Healthcare and Health Law.

The **types of articles** that we are publishing are original research, literature review, case reports, short communications, perspective/opinion/commentary manuscripts, and interviews. We do not exclude the manuscripts reporting negative results or those involving more than one specialty.

There is **no charge applicable** to authors for submission, processing and publishing the manuscripts.

Only manuscripts in **English** will be accepted.

The Journal of Medical and Radiological Oncology currently has **2 Issues/year.**

For more information on the Requirements, please visit our website: **www.jmedradonc.org**

Open Access Policy: Full Open Access

Cover: July is Cancer Survival month. Hope is there not only for colorectal cancer patients (see Editorial), but for all cancer patients, and we are here to hype the latest news.
Cover design: Dana & Erik Kolozsi (Rest Arh)

For advertising information please send an email to **office@jmedradonc.org**

ISSN 2784 – 0131
ISSN-L 2784 – 0131

Casa Cărţii de Ştiinţă
400129 Cluj-Napoca; B-dul Eroilor, nr. 6-8
Tel.: 0264-431920; www.casacartii.ro;
e-mail: editura@casacartii.ro

Journal of Medical and Radiation Oncology

Journal homepage: www.jmedradonc.org

TABLE OF CONTENTS

Interviews

Editorial

ASCO 2022 Cancer Cure: the Hype and the Hope

Finding a cure for cancer is a quest that motivates many young physicians and researchers to choose the Oncology field. Later, during his or her career, confronted with the reality of cancer, very often an oncologist feels like a despondent samurai that has to keep on fighting against all odds, outnumbered by a ruthless and devious enemy. Every time a cancer clinical trial or a new drug is introduced by media as a "cancer cure", I read the news with a mixture of hope and skepticism. Why skepticism? I distinctly remember two previous instances of "cancer cure" pep and hype sensationalist media announcements that made me believe for a moment that the unforeseen has happened. **First**, after several exceptional responses to angiostatin in a lung cancer mouse model, James Watson declared for the May 3d, 1998 edition of The New York Times that "Judah Folkman will cure cancer in 2 years". Unfortunately, the clinical trials using angiostatin in human lung cancer were not as successful and, the pharmaceutical company that Judah Folkman created, filed for bankruptcy. Few years later, the patents for angiostatin and endostatin, two angiogenesis inhibitors isolated by Folkman, were sold to China and, in 2018, Endostar (endostatin) was approved by China's State Food and Drug Administration (CFDA) for the treatment of non-small cell lung cancer. Folkman's brilliant idea to target angiogenesis was subsequently picked-up by other pharmaceutical companies and, several years later, bevacizumab and other anti-angiogenic drugs were developed and demonstrated clinical benefit in several cancer types. **Second**, three years later, in May 2001, the cover of Times Magazine announced the introduction of Gleevec in the treatment of chronic myeloid leukemia (CML) querying rhetorically whether Gleevec is "**the breakthrough** we've been waiting for". Well, yes, yes, and no. Yes, because Gleevec gave patients with CML a chance for long-term survival and even cure. Yes, because Gleevec became the herald of the tyrosine kinase inhibitors (TKIs) era that introduced in the oncology armamentarium dozens of targeted small molecules. No, because with the exception of CML and few other instances, after a period of initial response, TKIs induce therapeutic resistance in most types of cancer.

On June 5th, 2022 at the American Society of Oncology (ASCO) annual meeting, that took place in Chicago, a new "cancer cure" using dostarlimab, a PD-1 inhibitor was publicized. According to Dr. Andrea Cercek's ASCO presentation, all of the first 14 locally advanced rectal cancer patients enrolled in a neo-adjuvant dostarlimab clinical trial responded and none of them recurred during follow-up (range, 6 to 25 months). These results, published simultaneously on June 5th in the New England Journal of Medicine are stunning. 100% of the 14 patients treated

https://doi.org/10.53011/JMRO.2022.01.11

achieved complete remission that was maintained for at least one year in 50% of them. The resolution of symptoms was also very fast, occurring within 9 weeks of starting the treatment in 80% of the patients. A breakthrough? Of course. The toxicities associated with chemotherapy, radiotherapy or surgery were avoided in all the patients treated with dostarlimab. An important note though: all rectal tumors were mismatch-repair deficient, which made them particularly sensitive to immunotherapy. Another key point: only 5-10% of rectal cancers are mismatch-repair deficient and, therefore, this approach applies only to a minority of rectal cancer patients. In conclusion, at this time, it is premature to call dostarlimab the new standard of care treatment for locally advanced rectal cancer, as currently we do not know for how long these remarkable responses will be maintained. Regardless, the results are outstanding, and, clearly, they represent a proof of principle and are a breakthrough. Administering the right drug, in the right amount, to the right patient, at the right time may cure some forms of cancers. Personalized/precision treatments work in selected patients. ASCO 2022? A lot of glitter and hype, but also some real hope.

Doru Paul
Editor-in-Chief

JMRO

Journal of Medical and Radiation Oncology

Journal homepage: www.jmedradonc.org

GDF-15 Signaling Leading to Epithelial-to-Mesenchymal Transition in Colorectal Cancer - a Literature Review

Cristina Lungulescu[1], Daniel Sur[2,3], Ștefan Răileanu[4], Ștefania Maria Dumitru[4], Elena Adriana Dumitrescu[5], Cristian Virgil Lungulescu[6]

[1] Doctoral School, University of Medicine and Pharmacy, Craiova, Romania.
[2] Department of Medical Oncology, The Oncology Institute "Prof. Dr. Ion Chiricuţă", Cluj-Napoca, Romania.
[3] 11th Department of Medical Oncology, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania.
[4] Department of Oncology, Filantropia Clinical Hospital, Craiova, Romania
[5] "Prof. Dr. Al. Trestioreanu" Institute of Oncology, Bucharest, Romania
[6] University of Medicine and Pharmacy of Craiova, Department of Oncology, Craiova, Romania

Corresponding author: Daniel Sur; **e-mail**: dr.geni@yahoo.co.uk

Review Articles

Abstract

***Importance**:* The epithelial-mesenchymal transition (EMT) is a well-established process leading to metastasis, which is responsible for the majority of cancer-related deaths. EMT represents a critical step in the development of tumors, and is distinguishable through specific characteristics in tumor cells, such as the ability to invade and resist pharmacological treatments. Growth differentiation factor 15 (GDF-15) is a distinct member of the transforming growth factor β (TGF- β) superfamily which increases metastasis of cells both in vitro and in vivo by inducing EMT.

***Observations**:* High GDF-15 levels in certain cancers, including endometrial, prostate, pancreatic, and colorectal cancer (CRC), may be associated with poor clinical outcomes. Higher plasma concentrations of GDF-15 have been linked to an increased risk of developing CRC and colorectal CRC-related mortality prior to a diagnosis of CRC. It has been observed that surgical excision of CRC reduces serum GDF-15, which increases when the tumor progresses, and that monitoring serum levels after surgery may aid in the prediction of cancer recurrence. However, data showed that GDF-15 regulation promoted 5-Fluorouracil (5-FU) resistance in colon cancer and GDF-15 overexpression can re-sensitize 5-FU-resistant tumor cells to chemotherapy, suggesting that GDF-15 may function as a tumor suppressor gene in colon cancer.

https://doi.org/10.53011/JMRO.2022.01.01
2784 – 0131/Copyright 2022 The Author(s).

***Conclusions**:* Functional investigations of GDF-15's role in malignancy are scarce and disputed; prior findings indicate overexpression of GDF-15 in cancers, which contrasts GDF-15's potential role as a tumor suppressor. A thorough understanding of the regulatory mechanisms of EMT may lead to significant advancements in the treatment and prevention of cancer.

Keywords: *growth/differentiation factor-15, GDF-15, epithelial–mesenchymal transition, EMT, colorectal cancer, metastasis, prognostic.*

1. Introduction

Most colorectal cancers (CRCs) cases are sporadic and not passed down, even if inherited genetic predisposition plays a role in some cases. Early CRCs develop genetic and epigenetic alterations that allow for rapid cell growth, resulting in the invasive and metastatic characteristics of CRC (1).

Epithelial–mesenchymal transition (EMT) is a process by which epithelial cells differentiate into mesenchymal cells in response to normal or pathological stimuli (2). EMT has been shown to be strongly related with the dissemination of epithelial cell malignancies (3). Growth differentiation factor 15 (GDF-15), which appears in both intracellular and extracellular forms, is a divergent member of the transforming growth factor (TGF-β) superfamily. GDF-15 is broadly distributed in mammalian tissues and has several roles in a variety of illnesses, including inflammation, cancer, cardiovascular disease, and obesity (4).

Cancers with high GDF-15 levels, such as endometrial (5), prostate (6), pancreatic (7), and CRCs (8), may be linked to poor clinical outcomes. Although GDF-15 has been proposed as a target for CRC treatment (9, 10), its biological role remains undefined and findings regarding its biological functions and involvement in carcinogenesis are at times conflicting (11, 12).

2. Molecular mechanism of EMT in Colorectal Cancer

In EMT, epithelial cells acquire mesenchymal characteristics. Notable examples of EMT include embryonic development and organ formation (13), tissue repair and fibrosis (14), and cancer progression (15). Among the three types of EMT, the latter (type 3) is linked to the development of invasive or metastatic phenotype (16).

During EMT, tumor cells lose their apical–basal polarity, suffer disintegration of the tight junction, and reorganize their cytoskeletal architecture, allowing them to become invasive. Extracellular stimuli from the tumor microenvironment, such as growth hormones and inflammatory cytokines, as well as intra-tumor physical stressors such as hypoxia, are improperly regulated in cancer cells (17). Consequently, EMT programming allows tumor cells to efficiently metastasize by enabling them to readjust to the constantly shifting conditions of the tumor microenvironment.

The EMT process is executed by effector molecules, orchestrated by transcription factors (EMT core regulators), and initiated by external stimuli (EMT inducers) (18).

Most EMT effectors are subcellular structural proteins that dictate cellular phenotype. EMT is characterized by the downregulation of genes that encode cell junction proteins (E-cadherin, claudins and occludins) and activation of genes that produce mesenchymal adhesion-promoting proteins (vimentin, fibronectin and N-cadherin). Research suggests that stage III CRC with loss of E-cadherin expression has a dismal prognosis (19). Furthermore, overexpression of N-cadherin and fibronectin is associated with metastasis and a shorter overall survival in individuals with CRC (20, 21).

Developmental transcription factors that control epithelial and mesenchymal markers by influencing target genes or modulating their own expression are known as EMT core regulators. Increased expression of EMT-related transcription factors such as SNAIL, SLUG, TWIST1, TWIST2, ZEB, ZEB2, PROX1,

FOXC2, FOXQ1, FOXM1, and FOXC1, has been correlated with CRC invasiveness and metastasis (1).

Several factors have been identified as potential EMT inducers in CRC. These inducers alter EMT-transcriptional factors directly or indirectly, triggering a cascade of intracellular signaling events. Hypoxia-inducible factor 1 alpha (HIF-1), myocyte enhancer factor 2D (MEF2D) and transmembrane protease/serine 4 (TMPRSS4) can induce EMT by activating ZEB transcription factors, while nucleotide binding protein-like (NUBPL) can upregulate SNAIL expression. The WNT/β -Catenin signaling pathway, which has been linked to EMT in CRC, can be induced by other proteins such as serine–threonine kinase receptor-associated protein (STRAP) and tumor suppressor candidate 3 (TUCS3). TGF-signaling and EMT are also promoted by neuropilin-2 (NRP2), GDF-15, and formin like2 (FMNL2). Eukaryotic initiation factor 5A2 (EIF5A2) overexpression may trigger EMT through an unidentified mechanism possibly involving C-Myc and metastasis-associated protein 1 (MTA-1) (1, 22) (Figure 1).

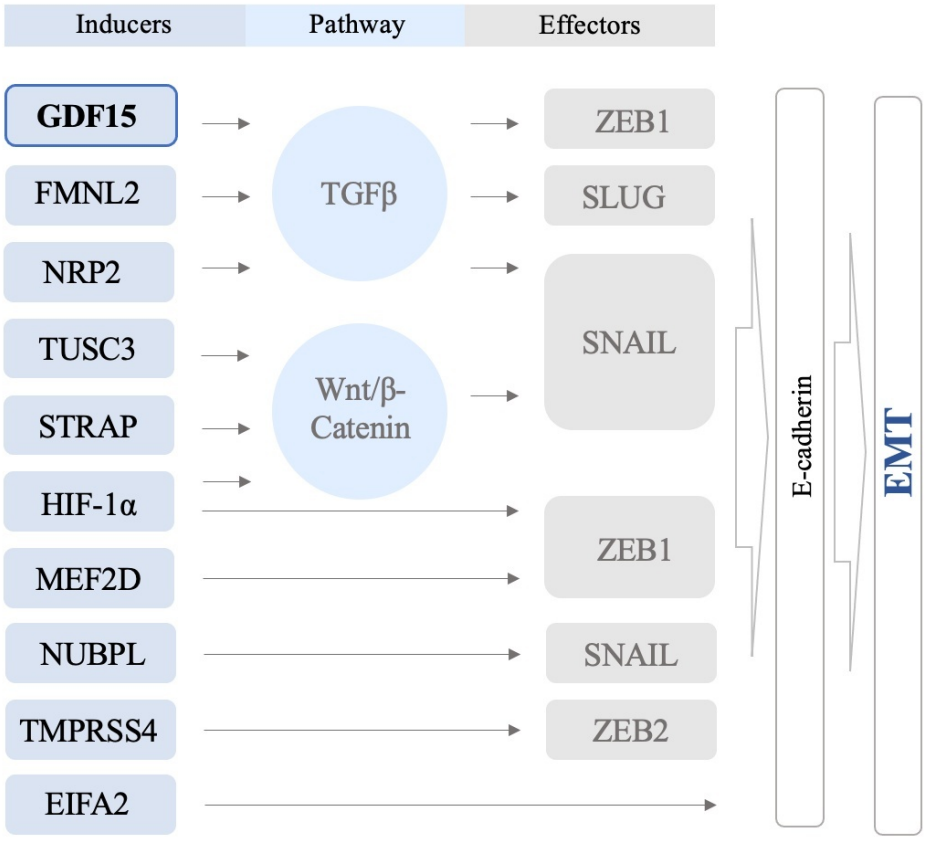


Fig. 1. Schematic of EMT induction
Adapted from "Regulation of EMT in Colorectal Cancer: A Culprit in Metastasis" by Vu T and Datta PK. *Cancers (Basel)*. 2017 Dec 16;9(12):171 (1)

3. Oncogenic role of GDF-15 in Colorectal Cancer

Growth/differentiation factor-15, also known as macrophage inhibitory cytokine 1, nonsteroidal anti-inflammatory drug-activated gene-1, placental bone morphogenetic protein, prostate-derived factor or placental transforming growth factor (PTGFB), was identified more than two decades ago as a distant member of the transforming growth factor (TGF) superfamily (23). In situ hybridization revealed that the human GDF-15 gene is positioned on chromosome 19p13.1–13.2. The GDF-15 genes in humans, rats, and mice are

comprised of two exons and one intron that interrupts the coding sequences in the pre-pro-domain of their respective proteins (4).

GDF-15 has been shown to suppress early tumor promotion under normal physiological settings. However, aberrant expression of this gene in advanced malignancies results in proliferation, invasion, metastasis, cancer stem cell production, immune evasion, and a diminished response to treatment (24). GDF-15 has been shown to promote tumor cell proliferation, survival, invasion, metastasis, and chemoresistance (12), and has been associated with the development of several malignancies, including cervical cancer, colorectal cancer, and multiple myeloma (8).

A recent study examined the impact of an inflammatory microenvironment on colon cancer invasion and metastasis in vitro and in vivo. Anti-GDF-15 antibody therapy inhibited colon cancer cell invasion and migration in vitro, demonstrating that GDF-15 participates in inflammation-induced invasiveness. Lipopolysaccharide-induced inflammation elevated GDF-15 production in vivo, while c-Fos deletion inhibited colon cancer cell lung metastasis in a mouse model. Similarly, colon cancer metastases and TNM stages were shown to be linked with c-Fos expression in patient samples. As a result, the study established that GDF-15 stimulated colon cancer invasion and metastasis through the extracellular signal-regulated kinase 1/2 (Erk1/2)/cFos signaling pathway (25).

The results of a multivariate Cox analysis revealed that serum GDF-15 is an independent prognostic factor for CRC. Cancer-specific survival was higher for individuals with lower GDF-15 serum levels, according to the results of another study (26).

Conversely, other findings suggest that GDF-15 may function as a tumor suppressor gene in the context of colon cancer (27).

4. Circulating GDF-15 as a biomarker

The AJCC TNM classification is the best predictor of CRC prognosis. Other prognostic indicators include poorly differentiated or high histological grade, vascular or lymphatic invasion, intestinal obstruction or perforation at diagnosis, and increased preoperative serum carcinoembryonic antigen presence (CEA) (28). However, due to the great degree of individual heterogeneity, an individual's chance of recurrence following therapy cannot be predicted properly (29). Allele loss of chromosome 18, microsatellite instability-deficient mismatch repair (MSI/dMMR) , and mutations in KRAS have been shown to negatively affect prognosis in cancer patients (30, 31). According to the research on EMT biomarkers, low expression of E-cadherin (32) and high expression of N-cadherin (21), Slug, and Vimentin (33) have been associated with a worse prognosis in CRC (34).

Several studies have attributed GDF-15 plasma levels to CRC diagnosis and death (11, 35, 36). High plasma levels of GDF-15 before diagnosis of CRC are related with an increased risk of CRC incidence and CRC-specific mortality, according to two significant cohorts evaluated in a prospective study, even after adjusting for other inflammatory indicators, risk factors, and clinical and pathological features (age, sex, tumor location, polyp history, tumor grade, or disease stage) (37).

Another study revealed that surgical excision of CRC decreases serum GDF-15, which was elevated in the context of tumor recurrence (26). Moreover, monitoring serum levels after surgery might help predict cancer recurrence. Further examination of the clinical significance of GDF-15 showed that serum levels are complementary to CEA and that GDF-15 is associated with the development or recurrence of CRC with liver metastases. However, GDF-15 blood concentrations were shown to be extremely variable in individuals with benign illness, indicating that serum levels should be read with caution (38), especially given the possibility of acute inflammation in CRC patients during chemotherapy (39).

Numerous articles have established that GDF-15 plays a critical function in tumor growth suppression, although they did not specifically study CRC.

One study tested the serum level of GDF-15 in 260 healthy blood donors as well as in 193 patients with adenomatous polyps or colon cancer. The study found that the Tumor-

Node-Metastasis (TNM) stage was associated with the level of GDF-15 serum (4, 40).

Both the pro-domain and mature domains of GDF-15 may have various biological functions, depending on the context in which they are expressed (41, 42). It's possible that during different phases of tumor evolution, these diverse forms may have contradictory purposes. In addition, GDF-15 may have varied roles in cancer depending on its intracellular location.

5. Resistance to chemotherapy

The conventional treatment for colon cancer is chemotherapy based on 5-fluorouracil (5-FU). Resistance to 5-FU is a major problem in clinical treatment, with much still unknown about the processes that allow colon cancer cells to become resistant to 5-FU treatment.

An investigation into whether 5-FU-resistant colon cancer cells undergo EMT and apoptosis, as well as the involvement of GDF-15 in controlling these processes revealed that 5-FU resistance in colon cancer was induced by suppression of GDF-15 and the downstream Smad signaling pathway. 5-FU-resistant human colon cancer cells/FU cells were created by exposing them to steadily increasing doses of 5-FU over time. Subsequently, HCT-15/FU cells resistant to 5-FU could be made susceptible to 5-FU by overexpressing GDF-15. Moreover, HCT-15/FU with decreased GDF-15 expression showed a more robust proliferation ability and metastatic propensity in vivo.

The findings suggest that the suppression of the Smad signaling pathway caused EMT in HCT-15/FU cells (via the modification of N-cadherin, E-cadherin, and MMP14 expression). The lack of E-cadherin in the HCT-15/FU group was further verified by in vivo tests (27).

6. Conclusion and outlook

The EMT is one of the most widely acknowledged of the pathways that lead to metastasis, which accounts for the majority of cancer-related fatalities. To complete the process of EMT, a complex network of molecular signaling channels and regulators must operate together.

Although GDF-15 has antitumor action in the early stages of carcinogenesis, it has been shown to significantly increase the rate of cancer invasion and metastasis in advanced stages of cancer. Functional investigations of GDF-15's role in malignancy are scarce and disputed: on one hand, the literature demonstrates overexpression of GDF-15 in cancers; on the other, GDF-15 has been found to act as a tumor suppressor.

To create optimal treatment methods for CRC, it is necessary to understand the fundamental underlying mechanisms behind these transformations, especially regarding how CRC cells gain invasive and metastatic features. Cancer treatment might benefit from a better comprehension of the EMT regulating mechanism. As yet, the involvement of GDF-15 in CRC metastasis and EMT is unclear.

Abbreviations:

5-FU - 5-fluorouracil
AJCC-American Joint Committee on Cancer
CEA - carcinoembryonic antigen
CRC - colorectal cancer
EIF5A2 - eukaryotic initiation factor 5A2
EMT - epithelial-to-mesenchymal transition
Erk1/2 - extracellular signal-regulated kinase 1/2
FMNL2 - formin-like2).
GDF-15 - growth/differentiation factor-15
HIF-1 - hypoxia-inducible factor 1 alpha
MEF2D - myocyte enhancer factor 2D
MIC-1 - macrophage inhibitory cytokine 1

MSI/dMMR - microsatellite instability-deficient mismatch repair
MTA-1 - metastasis-associated protein 1
NAG-1 - nonsteroidal anti-inflammatory drug-activated gene-1
NRP2 - neuropilin-2
NUBPL - nucleotide binding protein-like
PDF - prostate-derived factor
PLAB - placental bone morphogenetic protein
PTGFB - placental transforming growth factor
STRAP - serine–threonine kinase receptor-associated protein
TGF - transforming growth factor
TMPRSS4 - transmembrane protease/serine 4
TNM - Tumor, Node, Metastasis
TUCS3 - tumor suppressor candidate 3

Statements:

Author Contributions: CL and CVL conceived of the presented idea. EAM, SMD, SR collected the data. CL and CVL drafted the manuscript. DS performed critical revision of the article.

Consent for publication: As the corresponding author, I confirm that the manuscript has been read and approved for submission by all co-authors

Funding:This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

Conflicts of Interest: The authors declare no conflict of interest.

References:

1. Vu T, Datta P. Regulation of EMT in Colorectal Cancer: A Culprit in Metastasis. Cancers. 2017;9(12):171.

2. Chen T, You Y, Jiang H, Wang ZZ. Epithelial-mesenchymal transition (EMT): A biological process in the development, stem cell differentiation, and tumorigenesis. J Cell Physiol. 2017 Dec;232(12):3261-3272.

3. Lu W, Kang Y. Epithelial-Mesenchymal Plasticity in Cancer Progression and Metastasis. Dev Cell. 2019 May 6;49(3):361-374.

4. Emmerson PJ, Duffin KL, Chintharlapalli S, Wu X. GDF-15 and Growth Control. Front Physiol. 2018 Nov 27;9:1712.

5. Staff AC, Trovik J, Eriksson AG, Wik E, Wollert KC, Kempf T, Salvesen HB. Elevated plasma growth differentiation factor-15 correlates with lymph node metastases and poor survival in endometrial cancer. Clin Cancer Res. 2011 Jul 15;17(14):4825-33.

6. Brown DA, Lindmark F, Stattin P, Bälter K, Adami HO, Zheng SL, Xu J, Isaacs WB, Grönberg H, Breit SN, Wiklund FE. Macrophage inhibitory cytokine 1: a new prognostic marker in prostate cancer. Clin Cancer Res. 2009 Nov 1;15(21):6658-64.

7. Wang X, Li Y, Tian H, Qi J, Li M, Fu C, Wu F, Wang Y, Cheng D, Zhao W, Zhang C, Wang T, Rao J, Zhang W. Macrophage inhibitory cytokine 1 (MIC-1/GDF-15) as a novel diagnostic serum biomarker in pancreatic ductal adenocarcinoma. BMC Cancer. 2014 Aug 8;14:578.

8. Mehta RS, Song M, Bezawada N, Wu K, Garcia-Albeniz X, Morikawa T, Fuchs CS, Ogino S, Giovannucci EL, Chan AT. A prospective study of macrophage inhibitory cytokine-1 (MIC-1/GDF-15) and risk of colorectal cancer. J Natl Cancer Inst. 2014;106(4).

9. Yang MH, Kim J, Khan IA, Walker LA, Khan SI. Nonsteroidal anti-inflammatory drug activated gene-1 (NAG-1) modulators from natural products as anti-cancer agents. Life Sci. 2014 Apr 1;100(2):75-84.

10. Zhong Y, Krisanapun C, Lee SH, Nualsanit T, Sams C, Peungvicha P, Baek SJ. Molecular targets of apigenin in colorectal cancer cells: involvement of p21, NAG-1 and p53. Eur J Cancer. 2010 Dec;46(18):3365-74.

11. Wang X, Baek SJ, Eling TE. The diverse roles of nonsteroidal anti-inflammatory drug activated gene (NAG-1/GDF-15) in cancer. Biochem Pharmacol. 2013 Mar 1;85(5):597-606.

12. Mimeault M, Batra SK. Divergent molecular mechanisms underlying the pleiotropic functions of macrophage inhibitory cytokine-1 in cancer. J Cell Physiol. 2010 Sep;224(3):626-35.

13. Shook D, Keller R. Mechanisms, mechanics and function of epithelial-mesenchymal transitions in early development. Mech Dev. 2003 Nov;120(11):1351-83.

14. Kalluri R. EMT: when epithelial cells decide to become mesenchymal-like cells. J Clin Invest. 2009 Jun;119(6):1417-9.

15. Kang Y, Massagué J. Epithelial-mesenchymal transitions: twist in development and metastasis. Cell. 2004 Aug 6;118(3):277-9.

16. Singh A, Settleman J. EMT, cancer stem cells and drug resistance: an emerging axis of evil in the war on cancer. Oncogene. 2010 Aug 26;29(34):4741-51.

17. Thiery JP, Acloque H, Huang RY, Nieto MA. Epithelial-mesenchymal transitions in development and disease. Cell. 2009 Nov 25;139(5):871-90.

18. Tsai JH, Yang J. Epithelial-mesenchymal plasticity in carcinoma metastasis. Genes Dev. 2013 Oct 15;27(20):2192-206.

19. Yun JA, Kim SH, Hong HK, Yun SH, Kim HC, Chun HK, Cho YB, Lee WY. Loss of E-Cadherin expression is associated with a poor prognosis in stage III colorectal cancer. Oncology. 2014;86(5-6):318-28.

20. Saito N, Nishimura H, Kameoka S. Clinical significance of fibronectin expression in colorectal cancer. Mol Med Rep. 2008;1(1):77-81.

21. Yan X, Yan L, Liu S, Shan Z, Tian Y, Jin Z. N-cadherin, a novel prognostic biomarker, drives malignant progression of colorectal cancer. Mol Med Rep. 2015 Aug;12(2):2999-3006.

22. Dongre A, Weinberg RA. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. Nat Rev Mol Cell Biol. 2019 Feb;20(2):69-84.

23. Bootcov MR, Bauskin AR, Valenzuela SM, Moore AG, Bansal M, He XY, Zhang HP, Donnellan M, Mahler S, Pryor K, Walsh BJ, Nicholson RC, Fairlie WD, Por SB, Robbins JM, Breit SN. MIC-1, a novel macrophage inhibitory cytokine, is a divergent member of the TGF-beta superfamily. Proc Natl Acad Sci U S A. 1997 Oct 14;94(21):11514-9.

24. Fang L, Li F, Gu C. GDF-15: A Multifunctional Modulator and Potential Therapeutic Target in Cancer. Curr Pharm Des. 2019;25(6):654-662.

25. Ding Y, Hao K, Li Z, Ma R, Zhou Y, Zhou Z, Wei M, Liao Y, Dai Y, Yang Y, Zhang X, Zhao L. c-Fos separation from Lamin A/C by GDF-15 promotes colon cancer invasion and metastasis in inflammatory microenvironment. J Cell Physiol. 2020 May;235(5):4407-4421.

26. Wang X, Yang Z, Tian H, Li Y, Li M, Zhao W, Zhang C, Wang T, Liu J, Zhang A, Shen D, Zheng C, Qi J, Zhao D, Shi J, Jin L, Rao J, Zhang W. Circulating MIC-1/GDF-15 is a complementary screening biomarker with CEA and correlates with liver metastasis and poor survival in colorectal cancer. Oncotarget. 2017 Apr 11;8(15):24892-24901.

27. Wang B, Ma N, Zheng X, Li X, Ma X, Hu J, Cao B. GDF-15 Repression Contributes to 5-Fluorouracil Resistance in Human Colon Cancer by Regulating Epithelial-Mesenchymal Transition and Apoptosis. Biomed Res Int. 2020 Sep 28;2020:2826010.

28. Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton SR, Hammond ME, Henson DE, Hutter RV, Nagle RB, Nielsen ML, Sargent DJ, Taylor CR, Welton M, Willett C. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med. 2000 Jul;124(7):979-94.

29. Zafar SN, Hu CY, Snyder RA, Cuddy A, You YN, Lowenstein LM, Volk RJ, Chang GJ. Predicting Risk of Recurrence After Colorectal Cancer Surgery in the United States: An Analysis of a Special Commission on Cancer National Study. Ann Surg Oncol. 2020 Aug;27(8):2740-2749.

30. Kawakami H, Zaanan A, Sinicrope FA. Microsatellite instability testing and its role in the management of colorectal cancer. Curr Treat Options Oncol. 2015 Jul;16(7):30.

31. Deng Y, Wang L, Tan S, Kim GP, Dou R, Chen D, Cai Y, Fu X, Wang L, Zhu J, Wang J. KRAS as a predictor of poor prognosis and benefit from postoperative FOLFOX chemotherapy in patients with stage II and III colorectal cancer. Mol Oncol. 2015 Aug;9(7):1341-7.

32. Christou N, Perraud A, Blondy S, Jauberteau MO, Battu S, Mathonnet M. E-cadherin: A potential biomarker of colorectal cancer prognosis. Oncol Lett. 2017 Jun;13(6):4571-4576.

33. Toiyama Y, Yasuda H, Saigusa S, Tanaka K, Inoue Y, Goel A, Kusunoki M. Increased expression of Slug and Vimentin as novel predictive biomarkers for lymph node metastasis and poor prognosis in colorectal cancer. Carcinogenesis. 2013 Nov;34(11):2548-57.

34. Parisi E, Sorolla A, Montal R, González-Resina R, Novell A, Salud A, Sorolla MA. Prognostic Factors Involved in the Epithelial-Mesenchymal Transition Process in Colorectal Cancer Have a Preponderant Role in Oxidative Stress: A Systematic Review and Meta-Analysis. Cancers (Basel). 2020 Nov 11;12(11):3330.

35. Li C, Wang X, Casal I, Wang J, Li P, Zhang W, Xu E, Lai M, Zhang H. Growth differentiation factor 15 is a promising diagnostic and prognostic biomarker in colorectal cancer. J Cell Mol Med. 2016 Aug;20(8):1420-6.

36. Wallin U, Glimelius B, Jirström K, Darmanis S, Nong RY, Pontén F, Johansson C, Påhlman L, Birgisson H. Growth differentiation factor 15: a prognostic marker for recurrence in colorectal cancer. Br J Cancer. 2011 May 10;104(10):1619-27.

37. Mehta RS, Chong DQ, Song M, Meyerhardt JA, Ng K, Nishihara R, Qian Z, Morikawa T, Wu K, Giovannucci EL, Fuchs CS, Ogino S, Chan AT. Association Between Plasma Levels of Macrophage Inhibitory Cytokine-1 Before Diagnosis of Colorectal Cancer and Mortality. Gastroenterology. 2015 Sep;149(3):614-22.

38. Kim JM, Kosak JP, Kim JK, Kissling G, Germolec DR, Zeldin DC, Bradbury JA, Baek SJ, Eling TE. NAG-1/GDF-15 transgenic mouse has less white adipose tissue and a reduced inflammatory response. Mediators Inflamm. 2013;2013:641851.

39. Lee HN, Na HK, Surh YJ. Resolution of inflammation as a novel chemopreventive strategy. Semin Immunopathol. 2013 Mar;35(2):151-61.

40. Brown DA, Ward RL, Buckhaults P, Liu T, Romans KE, Hawkins NJ, Bauskin AR, Kinzler KW, Vogelstein B, Breit SN. MIC-1 serum level and genotype: associations with progress and prognosis of colorectal carcinoma. Clin Cancer Res. 2003 Jul;9(7):2642-50.

41. Bauskin AR, Zhang HP, Fairlie WD, He XY, Russell PK, Moore AG, Brown DA, Stanley KK, Breit SN. The propeptide of macrophage inhibitory cytokine (MIC-1), a TGF-beta superfamily member, acts as a quality control determinant for correctly folded MIC-1. EMBO J. 2000 May 15;19(10):2212-20.

42. Bauskin AR, Brown DA, Junankar S, Rasiah KK, Eggleton S, Hunter M, Liu T, Smith D, Kuffner T, Pankhurst GJ, Johnen H, Russell PJ, Barret W, Stricker PD, Grygiel JJ, Kench JG, Henshall SM, Sutherland RL, Breit SN. The propeptide mediates formation of stromal stores of PROMIC-1: role in determining prostate cancer outcome. Cancer Res. 2005 Mar 15;65(6):2330-6.

JMRO

Journal of Medical and Radiation Oncology

Journal homepage: www.jmedradonc.org

Gastric Signet Ring Cell Carcinoma: an Overview

Eugen Ursu[1]

[1] *Qomix, Bucharest, Romania*

Corresponding author: Eugen Ursu; **e-mail**: ursu_eugen@outlook.com

Abstract

Gastric signet ring cell carcinoma (GSRCC) is an important histological type of gastric cancer. Its biological and clinical particularities distinguish it from other gastric cancers in ways that require tailored clinical management and decision-making. This short review provides an overview of what is known about this prevalent clinical entity, highlights recent developments in the research surrounding GSRCC, and covers microbiome, immunology, computational pathology, and clinical research findings.

Keywords: *clinical-updates, gastric cancer, oncology-review, signet-ring-cell, carcinoma*

Review Articles

1. Introduction

The scope of this review is to briefly summarize what is known about the biology and clinical management of gastric signet ring cell carcinoma (GSRCC), as well as to highlight the recent developments and introduce recent reviews that cover several key topics in greater depth. We leveraged modern literature analytics technologies to interactively analyze the citation graph (https://www.researchrabbit.ai/) and identify novel developments in the field of GSRCC.

1.1. Epidemiology

According to GLOBOCAN 2018, stomach cancer is a prevalent cancer with high incidence (>1M new cases in 2018) and was responsible for an estimated 783,000 deaths in 2018 alone (1). Accordingly, gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of cancer death (1). Incidence rates are significantly higher in Eastern Asia in comparison to Northern America and Northern Europe (1).

In high-income countries, the incidence of gastro-esophageal junction cancers has increased (2). Recent studies highlight a decreased incidence rate for the intestinal subtype with non-cardial localization; however, there is increased incidence for both intestinal and Lauren diffuse histological subtypes in gastric cardia and gastro-esophageal junction (GEJ) (2–4).

The incidence of GSRCC has been on the rise, with incidence estimates in the US indicating an increase from 0.3 cases / 100,000 in 1973 to 1.8 cases / 100,000 in 2000 (3). This increase

https://doi.org/10.53011/JMRO.2022.01.02
2784 – 0131/Copyright 2022 The Author(s).

Published by Casa Cărții de Știință

happened concurrently with a significant evolution of the histological classification of gastric adenocarcinoma, resulting in the hypothesis that the increase could largely be explained by the increased explicit representation of GSRCC in histological classifications that are widely clinically used. Since 1990, GSRCC has been represented in the WHO classification for gastric cancers as a separate histological type (5).

There are clinical features of GSRCC that are different from those of other gastric adenocarcinomas. For the stomach and GEJ, GSRCC presents at a younger age, at an advanced stage, with lymphatic spread, peritoneal metastasis, rapid progression, and is generally predominant in females (2). There has been much controversy regarding the prognostic value of GSRCC, due to inconsistent results, however, recent research has shown that, for early-stage gastric and GEJ cancer, GSRCC is correlated with better survival in comparison to non-signet cell tumors, whereas the reverse is true for advanced stages (2). For excellent reviews with more coverage of presentation and risk factors, as well as other aspects, see (2,5).

1.2. Classification

It is important to understand where GSRCC resides within the histological classification of gastric adenocarcinomas. Before 1990, GSRCC was not treated as a distinct histological subtype. Instead, it was included within other categories: diffuse by Lauren, infiltrative subtype by Ming, undifferentiated by Nakamura classification, and high grade by The Union International of Cancer Control (UICC) (5). All the enumerated types of tumors are aggressive, suggesting that although GSRCC was not allocated a distinct histological class prior to 1990, it was nevertheless classed within an aggressive family of tumors. Currently, the WHO classification of tumors of the digestive system (6) defines GSRCC as a loosely cohesive adenocarcinoma composed of cancer cells with a mucin-rich cytoplasm and an eccentric, crescent-shaped nucleus. (Fig. 1A).

Molecular classifications for gastric cancers are well-established and include various classifications i.e. intrinsic subtypes, Lei subtypes, The Cancer Genome Atlas (TCGA) subtypes and Asian Cancer Research Group (ACRG) subtypes (7–9).

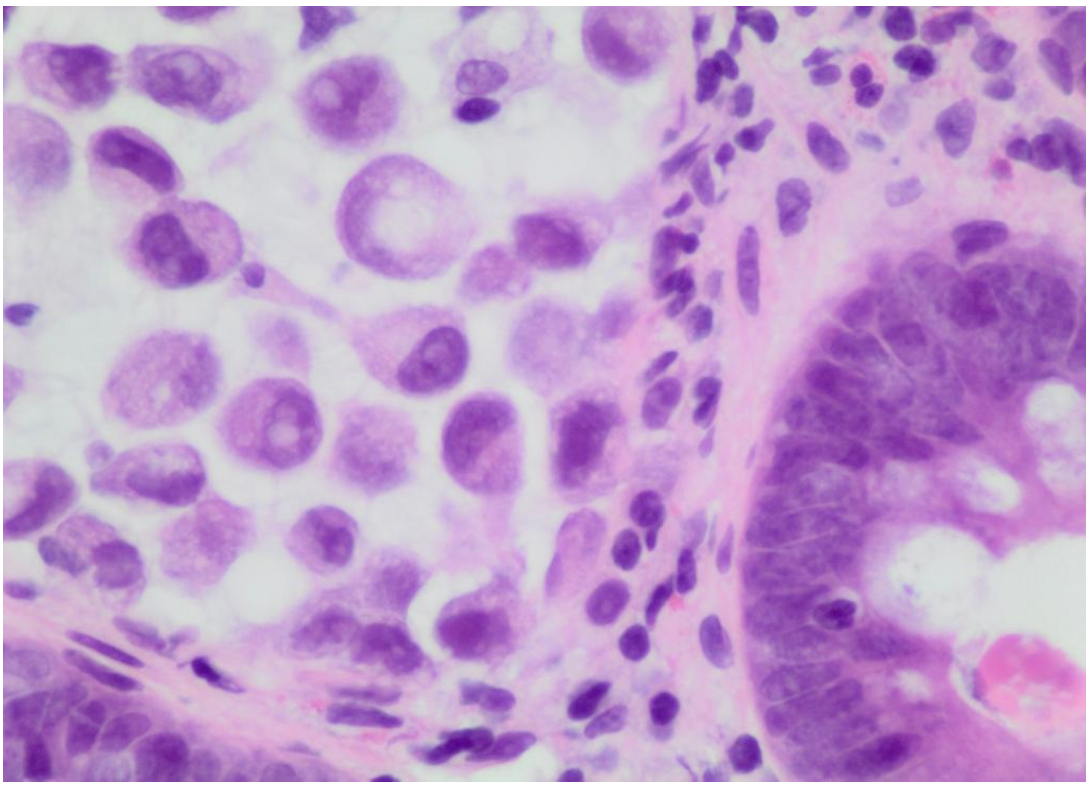


Figure 1A. Gastric signet-cell carcinoma H&E x 40. Image courtesy of Prof. Diana Ionescu - University of British Columbia, Vancouver

The inclusion of GSRCC within a molecular subtype is somewhat inconclusive, possibly due to the fundamental incompatibilities between histological and molecular classifications. Nevertheless, the study that defined the ACRG classification (9), observed that 43.5% of GSRCC belonged to the microsatellite stable/ epithelial-to-mesenchymal transition (MSS/ EMT) molecular subtype, while 8.4% belonged to MSS/TP53$^-$ with other molecular subtypes covering <7%. Although the association was not statistically significant, possibly because of the low sample size for this histological type (37 GSRCC patients). The MSS/EMT subtype by ACRG is closest to the genomically stable subtype of the TCGA classification (10). Including GSRCC in the predominant molecular subtypes of both classifications suggests that it exhibits specific molecular features. Namely, GSRCC bears low mutational load and loss-of-function mutations in cadherin 1 gene (CDH1). The clinical features implied by the molecular classifications are consistent with the observed clinical features of GSRCC, i.e. younger age of presentation, the worst prognosis coinciding with advanced stage GSRCC, and high recurrence rate.

1.3. Molecular alterations

The main pathological hallmarks of GSRCC are cytoplasmic mucin accumulation and decrease in cell-cell adhesion. GSRCC is generally associated with germline mutations in the *CDH1* gene whose product, E-cadherin, is involved in intercellular junctions in epithelia. Radical total gastrectomy with extensive lymphadenectomy is required for patients with *CDH1* mutations (2). Moreover, somatic loss of E-cadherin is characteristic of signet ring cell tumors in multiple organs and has been associated with EMT, a process that is essential to disease progression. E-cadherin loss has been observed to occur early in the progression of GSRCC (2). An interesting question is whether mucin accumulation is a consequence of other oncogenic processes or whether the mucin accumulation itself drives the disease. The latter possibility is supported by strong evidence from mechanistic studies which have identified a positive feedback loop in which mucin 4 activates the ERBB2/ERBB3 complex which, via multiple molecular intermediaries, leads to the loss of junctions and production of mucins (thereby forming the loop), leading to the formation of signet cancer cells (11). Gain-of-function mutations in *RhoA* are specific to the genomically stable molecular subtype of TCGA classification (10), which is the molecular subtype primarily associated with GSRCC. For an excellent recent review that explores in a greater depth molecular alterations, including alterations in other genes, gene fusions, miRNAs, methylation and histone modifications, the reader is referred to (2).

1.4. Clinical management

There are no currently available high-impact and high-confidence recommendations specifically for the clinical management of GSRCC (12). Clinical management is different in early GSRCC and advanced GSRCC or GEJ signet ring cell carcinoma (13), with significant differences in survival: the estimated 5-year overall survival rate in early gastric cancer with signet ring cells is 90.7% and 83.2% in non-signet ring cell carcinoma; for advanced gastric cancer, the estimated survival rate with signet ring cells is 32.1% and 37.9% in non-signet ring cancers. (13). In terms of clinical presentation (13), GSRCC was found to comprise 22.5% of early gastric cancers and, 26.5% of advanced gastric cancers. Note that the presented results originate from the Department of Surgery at Taipei Veterans General Hospital, which could explain the overall higher survival values versus other geographic regions ((The Surveillance Epidemiology, End Results (SEER)) database, an authoritative source of cancer statistics in the US, reports a 27.5% 5-year overall survival rate for GSRCC (Tang et al. 2020)). For recent reviews that detail clinical management, the reader is referred to (2,12,14).

The recommended treatment for early GSRCC is surgery, and endoscopic methods are employed in select cases. This line of treatment differs from that of general early gastric cancers, where endoscopic resection is a recommended option alongside definitive surgery. An important question is whether the

survival rate of early GSRCC is better due to specifics of its tumor biology or other confounding factors. It has been suggested that the better outcomes in early GSRCC with respect to non-signet ring cell gastric cancers could be due to earlier presentation, mucosal restriction of the tumor, and less frequent lymph node invasion (2,5). This suggests that signet ring cell histology is not necessarily an independent predictor for survival. Instead, it appears to be related to survival due to confounding variables such as age of presentation.

Treatment of advanced GSRCC (which is defined by mucosal invasion) is challenging. Although gastrectomy with radical lymph node dissection (D2) is recommended, the role of chemotherapy is not well established (2). In general, perioperative chemotherapy is recommended for advanced gastric cancer (15), but due to the unclear chemosensitivity of GSRCC, it is not clear whether neoadjuvant therapy brings more benefits than the risk of significant disease progression due to the delay of surgery (2). This is supported by studies that have reported no survival benefit from perioperative chemotherapy (16). On the other hand, other studies indicate improved outcomes of neoadjuvant therapy, such as the FLOT4 trial (17), which included a significant proportion of GSRCC cases among all gastric cancer patients, while another study showed improved outcomes in signet ring cell esophagogastric adenocarcinomas (18). Clinical management of advanced GSRCC would greatly benefit from further research into clarifying which treatment algorithms are optimal.

2. Developments

In the following section, we highlight some of the more recent developments in the research of GSRCC biology and clinical management.

2.1. Microbiome

Recent evidence showing the involvement of microbiota in gastric carcinogenesis (19) is not surprising given that the microbiota is beginning to be considered a metabolically active organ (20). Notably, in a recent study (20), investigations have begun delving into the microbiota differences among subtypes of gastric cancer. The authors separately analyzed formalin-fixed paraffin-embedded (FFPE) samples from GSRCC and adenocarcinoma through 16S rRNA analysis. A major result of the study is that there are significant microbial composition differences among GSRCC and gastric adenocarcinoma, differences which could eventually become microbial biomarkers of disease. The phyla Fusobacteria, Bacteroidetes, Patescibacteria, and BC1 were significantly enriched in GSRCC in comparison to gastric adenocarcinoma (20). The authors note that Fusobacteria and Bacteroidetes, phyla which include anaerobic bacteria, have been observed to be enriched in some cancers, including oral and head cancers (20). Fusobacteria could become an important biomarker for GSRCC. Interestingly, the authors evaluated the differences in active microbial metabolic pathways that are implied by the differences in microbial composition. This led to the observation that the pyrimidine biosynthesis pathway is employed by the microbial community that is specific to GSRCC. Pyrimidine metabolism pathways, which have been associated with progression in lung and breast cancer, could therefore represent specific targets within the microbiota in GSRCC r (20,21). Multiple recent emerging reviews cover the exciting area of cancer-related microbiome research (22–24).

2.2. Immunoregulatory landscape

A recent study measured serum levels of certain immunoregulatory molecules (GITR, OX40L and programmed cell death protein 1 PD-1) and identified a 1.25-fold increase in soluble GITR (sGITR) in GSRCC in comparison to adenocarcinomas, suggesting that this could become a marker for discriminating GSRCC (26). Biologically, GITR is expressed on some regulatory T cells (Tregs) and is a co-stimulatory molecule. Clinical trials have attempted to use GITR agonists to inhibit suppressive Tregs in combination with other compounds used as immunotherapies. More broadly, a recent study that explored predictive factors for response to immunotherapy

(specifically anti-PD-L1 therapy) found that the presence of signet ring cancer cells correlates with non-responder status to PD-L1 targeting: within the GSRCC cases, only 1 responder and 18 non-responders to PD-L1 targeting (27). Nevertheless, the authors highlight that there are only a few reports on the clinical impact of immune checkpoint inhibitor markers on signet ring cells in gastric cancer (27). A 2017 study (28) reports an association between signet ring cancer cells and PD-L1, although the association did not appear to affect prognosis. This foreground the observations of Noh et al, who bring evidence for the high association between non-response status and signet ring cancer cells histology. A likely explanation for the low response rates of immune checkpoint inhibitors in this disease is a low total mutational burden.

2.3. Lymph node metastasis

Early gastric carcinoma (not necessarily GSRCC) is often treated with endoscopic resection, but it is important to perform an evaluation for the requirement of surgery after endoscopic resection. This further requires an assessment of lymph node metastasis likelihood. Conventionally, tumor budding (TB, traditionally defined as isolated single cancer cells or <5 cancer cells in the invasive front (29)) is used for evaluation. Nevertheless, a recent study (29) developed a modified tumor budding (mTB) scoring system as a better independent predictor for lymph node metastasis. mTB is evaluated similarly to TB, the difference being in that mTB excludes signet ring cells from its budding evaluation. The authors argue for excluding signet ring cells on the basis that early stage GSRCC has shown favorable survival (29).

Another study (30) developed a novel preoperative biomarker for predicting lymph node metastasis of GSRCC. The authors show that the derived monocyte to lymphocyte ratio (dMLR = monocyte count / (white blood cell count - neutrophil count)) is an independent predictor of lymph node metastasis and exhibits 60.3% sensitivity and 72.2% specificity, making it a potentially promising biomarker.

2.4. Response to neoadjuvant therapy

A recent study (31) brings further evidence for the association between the presence of signet ring cancer cells and the decreased likelihood of response to standard regimens of neoadjuvant therapy. The authors note that gastric cancer is a heterogeneous disease and that the current approach does not rely on patient selection, but rather on administering broad clinical trial-based regimens to all patients, which is likely leading to many patients not benefiting from neoadjuvant chemotherapy (31). It is therefore suggested that further efforts should be taken to develop methods for effectively predicting response to neoadjuvant therapy.

2.5. Clinicopathological characteristics, prognosis and treatments

An interesting study (25) sheds new light on the impact of GSRCC histology on prognosis, a question which, as previously noted, confused the field due to unsatisfactory and contradictory results. The single-center study investigated the issue by comparing mucinous gastric cancer (a rare histological subtype) and GSRCC, and observed that patients with GSRCC have overall worse survival rates, but that mucinous gastric cancer was predictive of poorer prognosis at an early stage (25), which is consistent with the more general tendency that has been observed when comparing GSRCC to other gastric cancers. The differences were observed when comparing cancer-specific survival (CSS), as opposed to overall survival (OS).

Another recent study reevaluates GSRCC clinicopathological data (32) in order to attempt to clarify some of the more controversial findings, including some of those discussed in this text. The study brings solid evidence to further support that there are distinct features that separate GSRCC from gastric adenocarcinoma. Moreover, independent prognostic factors are inferred: age, T stage, N stage, surgery, tumor size and tumor site (32). Being independent, these factors are effectively employed into the design of a nomogram for predicting overall survival with high accuracy. Nomograms are

commonly used tools in oncology and medicine (33) that allow for rapid and user-friendly computation, e.g. of probabilities and scores. Wei et. al show that GSRCC occurs more frequently in the middle and lower stomach region and that GSRCC is more likely to have bone metastasis (in comparison to other gastric cancers, which tend to have liver and lung metastasis). Importantly, the study found that signet ring cancer cell histology is not independently associated with mortality when disease stage is controlled for, in which case signet ring cell carcinoma is not more aggressive than differentiated cancers (32).

There is a lack of consensus on the optimal non-surgical treatment of GSRCC. This is compounded by the observed lack of chemosensitivity of GSRCC. Therefore, a promising direction is the exploration of targeted therapies for approaching pathways relevant to GSRCC, such as EMT, through chemical inhibitors, monoclonal antibodies or other targeting approaches (12). One active clinical trial has been identified on clinicaltrials.gov (ID NCT03355612) that explores XELOX (oxaliplatin with capecitabine) vs Apatinib with XELOX. Apatinib is a tyrosine kinase inhibitor targeting VEGFR2 that has been previously explored in metastatic gastric adenocarcinoma.

2.6. Classification in whole slide images

Due to cellular morphology and diffuse invasion, GSRCC tends to be more difficult to detect by pathologists (34) (Fig.1B). More precisely, false negatives may occur because of signet ring cancer cells' resemblance to crushed oxyntic glands, crushed mucous neck cells, goblet cells of intestinal metaplasia, and gastric xanthoma (34). In this regard, computational pathology has made progress in developing assistive tools to improve GSRCC detection by pathologists. These efforts have been facilitated by the increasing digitization of Haematoxilin and Eosin slides into whole slide images (WSIs). A recent study (34) successfully developed a deep learning system for signet ring cell carcinoma WSI classification (ROC-AUC = 0.99). The tool has good performance, and can highlight regions with high density of signet ring cancer cells on top of WSI, allowing for interpretation of the tool's output and assisting pathologists by guiding the focus to specific regions that are more likely to harbor signet ring cancer cells.

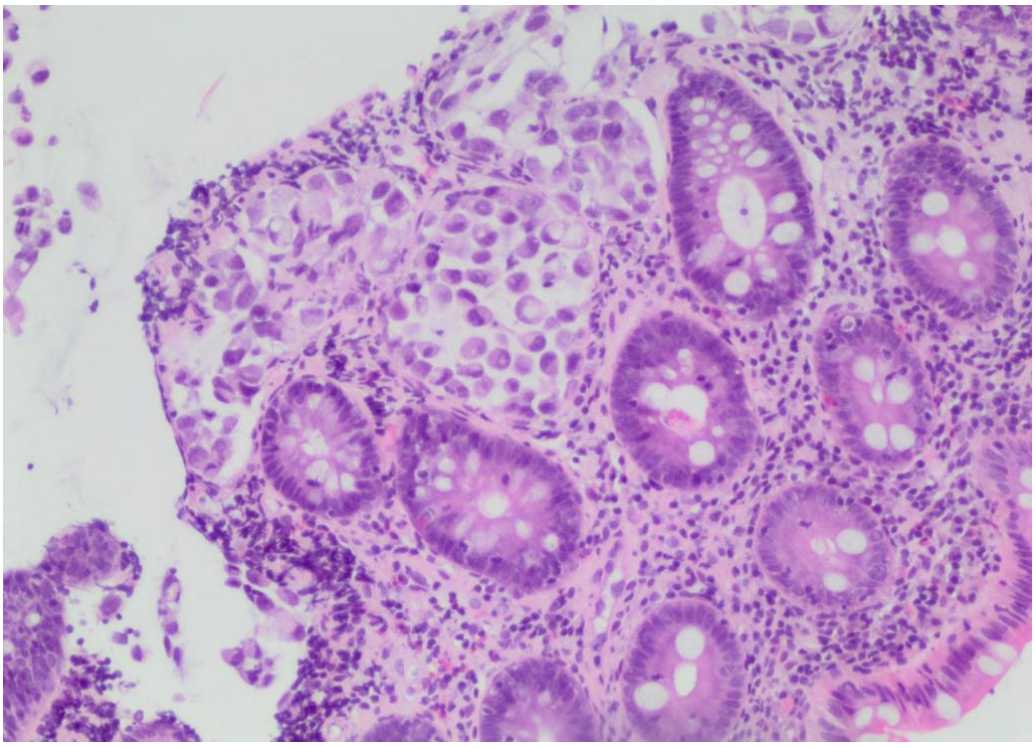


Figure 1B. Gastric signet-cell carcinoma H&E x 10. Image courtesy of Prof. Diana Ionescu - University of British Columbia, Vancouver

3. Conclusion

Research into gastric signet ring cell carcinoma is on the rise, with 135 research papers published in 2021 alone, as identified using PubMed. Comprising an estimated 16.9% of all gastric cancers (35), it remains a prevalent clinical entity that distinguishes itself from other gastric cancers and identifies a population of high unmet medical need and thus requires further results for guiding optimal.

Abbreviations:
ACRG - Asian Cancer Research Group
CSS - cancer-specific survival
dMLR - derived monocyte count to lymphocite ratio
EMT - epithelial-mesenchymal transition
FFPE - formalin-fixed, paraffin-embedded
GEJ - gastroesophageal junction
GSRCC - gastric signet ring cell carcinoma
MSS - microsatellite-stable
OS - overall survival
ROC-AUC - area under the curve for receiver operating characteristic curve
PD-1 - programmed cell death protein 1
SEER - surveillance, epidemiology, end results
TCGA - The Cancer Genome Atlas
TNM - Tumor, nodes, metastasis classification of malignant tumors
Tregs - regulatory T cells
UICC - The Union International of Cancer Control
U.S.- United States
VEGFR - vascular endothelial growth factor receptor
WSI - whole slide images

Statements:
Author's contribution: EU contributed to the design of the study, the data analysis and the writing of the article.
Previous publication: I declare that this paper was not published nor was submitted to be reviewed for publication in another journal.
Conflict of interest: I declare having no competing interests associated with this publication.
Funding Sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394–424.

2. Kumar NAN, Jose A, Usman N, Rajan K, Munisamy M, Shetty PS, et al. Signet ring cell cancer of stomach and gastro-esophageal junction: molecular alterations, stage-stratified treatment approaches, and future challenges. Langenbecks Arch Surg. 2022 Feb;407(1):87–98.

3. Henson DE, Dittus C, Younes M, Nguyen H, Albores-Saavedra J. Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973-2000: increase in the signet ring cell type. Arch Pathol Lab Med. 2004 Jul;128(7):765–70.

4. Mengardo V, Treppiedi E, Bencivenga M, Dal Cero M, Giacopuzzi S. Tailored treatment for signet ring cell gastric cancer. Updates Surg. 2018 Jun 9;70(2):167–71.

5. Pernot S, Voron T, Perkins G, Lagorce-Pages C, Berger A, Taieb J. Signet-ring cell carcinoma of the stomach: Impact on prognosis and specific therapeutic challenge. World J Gastroenterol. 2015 Oct 28;21(40):11428–38.

6. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. WHO classification of tumours of the digestive system. 2010;

7. Wang Q, Liu G, Hu C. Molecular classification of gastric adenocarcinoma. Gastroenterology Res. 2019 Dec;12(6):275–82.

8. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014 Sep 11;513(7517):202–9.

9. Cristescu R, Lee J, Nebozhyn M, Kim K-M, Ting JC, Wong SS, et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. Nat Med. 2015 May;21(5):449–56.

10. Ajani JA, Lee J, Sano T, Janjigian YY, Fan D, Song S. Gastric adenocarcinoma. Nat Rev Dis Primers. 2017 Jun 1;3:17036.

11. Fukui Y. Mechanisms behind signet ring cell carcinoma formation. Biochem Biophys Res Commun. 2014 Aug 8;450(4):1231–3.

12. Machlowska J, Pucułek M, Sitarz M, Terlecki P, Maciejewski R, Sitarz R. State of the art for gastric signet ring cell carcinoma: from classification, prognosis, and genomic characteristics to specified treatments. Cancer Manag Res. 2019 Mar 15;11:2151–61.

13. Kao Y-C, Fang W-L, Wang R-F, Li AF-Y, Yang M-H, Wu C-W, et al. Clinicopathological differences in signet ring cell adenocarcinoma between early and advanced gastric cancer. Gastric Cancer. 2019 Mar;22(2):255–63.

14. Machlowska J, Baj J, Sitarz M, Maciejewski R, Sitarz R. Gastric cancer: epidemiology, risk factors, classification, genomic characteristics and treatment strategies. Int J Mol Sci. 2020 Jun 4;21(11).

15. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006 Jul 6;355(1):11–20.

16. Messager M, Lefevre JH, Pichot-Delahaye V, Souadka A, Piessen G, Mariette C, et al. The impact of perioperative chemotherapy on survival in patients with gastric signet ring cell adenocarcinoma: a multicenter comparative study. Ann Surg. 2011 Nov;254(5):684–93; discussion 693.

17. Al-Batran S-E, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet. 2019 May 11;393(10184):1948–57.

18. Heger U, Sisic L, Nienhüser H, Blank S, Hinz U, Haag GM, et al. Neoadjuvant Therapy Improves Outcomes in Locally Advanced Signet-Ring-Cell Containing Esophagogastric Adenocarcinomas. Ann Surg Oncol. 2018 Aug;25(8):2418–27.

19. Hu Y-L, Pang W, Huang Y, Zhang Y, Zhang C-J. The gastric microbiome is perturbed in advanced gastric adenocarcinoma identified through shotgun metagenomics. Front Cell Infect Microbiol. 2018 Dec 12;8:433.

20. Ravegnini G, Fosso B, Saverio VD, Sammarini G, Zanotti F, Rossi G, et al. Gastric Adenocarcinomas and Signet-Ring Cell Carcinoma: Unraveling Gastric Cancer Complexity through Microbiome Analysis-Deepening Heterogeneity for a Personalized Therapy. Int J Mol Sci. 2020 Dec 20;21(24).

21. Cheng C, Wang Z, Wang J, Ding C, Sun C, Liu P, et al. Characterization of the lung microbiome and exploration of potential bacterial biomarkers for lung cancer. Transl Lung Cancer Res. 2020 Jun;9(3):693–704.

22. Wen J, Lau HC-H, Peppelenbosch M, Yu J. Gastric Microbiota beyond H. pylori: An Emerging Critical Character in Gastric Carcinogenesis. Biomedicines. 2021 Nov 12;9(11).

23. Bakhti SZ, Latifi-Navid S. Interplay and cooperation of Helicobacter pylori and gut microbiota in gastric carcinogenesis. BMC Microbiol. 2021 Sep 23;21(1):258.

24. Yang J, Zhou X, Liu X, Ling Z, Ji F. Role of the gastric microbiome in gastric cancer: from carcinogenesis to treatment. Front Microbiol. 2021 Mar 15;12:641322.

25. Tang C-T, Chen Y, Zeng C. Prognostic analysis of gastric signet ring cell carcinoma and mucinous carcinoma: a propensity score-matched study and competing risk analysis. Aging (Albany NY). 2020 Nov 20;12(21):22059–77.

26. Horozoglu C, Sonmez D, Kucukhuseyin O, Demirkol S, Hakan MT, Arikan S, et al. The importance of sPD-1, sOX40L and sGITR in terms of clinicopathology and histopathology in gastric cancer. Turk J Bioch. 2021 Jul 16;46(3):273–9.

27. Noh M-G, Yoon Y, Kim G, Kim H, Lee E, Kim Y, et al. Practical prediction model of the clinical response to programmed death-ligand 1 inhibitors in advanced gastric cancer. Exp Mol Med. 2021 Feb 5;53(2):223–34.

28. Jin S, Xu B, Yu L, Fu Y, Wu H, Fan X, et al. The PD-1, PD-L1 expression and CD3+ T cell infiltration in relation to outcome in advanced gastric signet-ring cell carcinoma, representing a potential biomarker for immunotherapy. Oncotarget. 2017 Jun 13;8(24):38850–62.

29. Yim K, Jang WM, Lee SH. Modified Tumor Budding as a Better Predictor of Lymph Node Metastasis in Early Gastric Cancer: Possible Real-World Applications. Cancers (Basel). 2021 Jul 7;13(14).

30. Tong C, Wang W, Xia Y, He C. A potential novel biomarker in predicting lymph node metastasis of gastric signet ring cell carcinoma: A derived monocyte to lymphocyte ratio. Am J Surg. 2021 Oct 21;

31. Rajabnejad A, Vaida F, Valasek M, Razzaque S, Fanta P, Horgan S, et al. Predictors and significance of histologic response to neoadjuvant therapy for gastric cancer. J Surg Oncol. 2021 May;123(8):1716–23.

32. Wei Q, Gao Y, Qi C, Yuan X, Li J, Xu Q, et al. Clinicopathological Characteristics and Prognosis of Signet Ring Gastric Cancer: A Population-Based Study. Front Oncol. 2021 Aug 13;11:580545.

33. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol. 2015 Apr;16(4):e173-80.

34. Kanavati F, Ichihara S, Rambeau M, Iizuka O, Arihiro K, Tsuneki M. Deep learning models for gastric signet ring cell carcinoma classification in whole slide images. Technol Cancer Res Treat. 2021 Dec;20:15330338211027900.

35. Benesch MGK, Mathieson A. Epidemiology of signet ring cell adenocarcinomas. Cancers (Basel). 2020 Jun 11;12(6).

JMRO

Journal of Medical and Radiation Oncology

Journal homepage: www.jmedradonc.org

Real-World Single-Center Clinical Data on Sorafenib in Patients with Unresectable Hepatocellular Carcinoma

Cătălin Ștefan Ghenea[1], Ștefania Dumitrescu[2], Livia Marieta Negoiță[1], Mariana Mihăilă[3], Livia Carmen Albu[3], Gabriel Constantinescu[1,4]

[1]*Clinical Department of Gastroenterology, Bucharest Emergency Clinical Hospital, Romania*
[2]*Department of Oncology, Fundeni Clinical Institute, Bucharest, Romania*
[3]*Center of Internal Medicine, Fundeni Clinical Institute, Bucharest, Romania*
[4]*University of Medicine and Pharmacy Carol Davila Bucharest, Romania*

Corresponding author: Ștefania Dumitrescu; **e-mail**: dr.stefaniadumitrescu@gmail.com

Abstract

Introduction. Hepatocellular carcinoma (HCC) is a malignant tumor that frequently develops in conjunction with chronic liver disease and cirrhosis, and is often identified late in its course, with a median survival of around 6 to 20 months following diagnosis. Although surgical excision is the gold standard of treatment, most patients are ineligible due to tumor size or underlying liver disease. The hepatic reserve of the patient, as determined by the Child-Turcotte-Pugh classification, frequently influences treatment options.

Method. Between January 2016 and June 2018, 42 patients admitted to Fundeni Clinical Institute's Department of Medical Oncology who had previously been treated with Sorafenib for more than two months were recruited in this retrospective analysis. We evaluated the etiology and stage of illness (BCLC), residual liver function (CHILD), performance status (ECOG), treatment response and side effects, progression-free survival, and overall survival.

Results. The study group had good short and long-term outcomes: median progression-free survival was 7.7 months and median overall survival was 11.6 months. The most frequently-reported adverse effects were skin rashes, diarrhea, hypertension, and hand-foot skin reaction.

Conclusion. This retrospective, single-center study confirmed the benefit of sorafenib in the treatment of advanced HCC, particularly in patients with good liver function and performance status.

Keywords: *Sorafenib, hepatocellular carcinoma, BCLC stage, ECOG performance status, overall survival, progression free survival.*

Original Research

https://doi.org/10.53011/JMRO.2022.01.03

1. Introduction

According to World Health Organization (WHO), hepatocellular carcinoma (HCC) is one of the most common malignancies, being the sixth most common cancer worldwide and the fourth leading cause of cancer-related deaths. There are around 841.000 new cases diagnosed every year, with an increasing incidence globally and 782.000 HCC-related deaths annually (1).

Major risk factors for HCC include cirrhosis (regardless of etiology), chronic infection with the hepatitis B virus (HBV) or hepatitis C virus (HCV), foods that are contaminated with aflatoxins, nonalcoholic fatty liver disease (obesity, diabetes and/or insulin resistance), alcohol consumption and smoking (2).

Hepatectomy can be used for patients with early-stage HCC. However, these cases are less common because patients with HCC often present with advanced-stage disease. Consequently, many of them require systemic therapies or palliative treatment (3).

Sorafenib is a tyrosine kinase inhibitor with activity against many protein kinases (RAF kinases), vascular endothelial growth factor receptors (VEGFR) and platelet-derived growth factor receptor (PDGFR), which also blocks tumor cell proliferation and tumor angiogenesis (4).

Sorafenib is generally well tolerated, with a manageable side effect profile. Diarrhea and hand-foot skin reaction are the most common side effects (5). The efficiency of sorafenib in patients with unresectable HCC has been evaluated in several clinical trials. In registration trials, sorafenib improved median overall survival (OS) in patients with advanced HCC by a median of 2.3-2.8 months (6,7). In the SHARP study, a randomized controlled trial, the median OS in the sorafenib-treated group was 10.7 months compared with 7.9 months in the placebo group, with a good safety profile (7). Based on the results of the two landmark trials (6,7), sorafenib is indicated only in patients with good liver function (Child-Pugh A) and advanced tumors (Barcelona Clinic Liver Cancer (BCLC) C) or intermediate stage tumors (BCLC B) who are not eligible or who progressed after locoregional therapy. However, sorafenib is sometimes used outside of these criteria in the real-world setting, mainly due to the absence of alternative treatment options (8,9). As these patient subgroups were not evaluated in registration trials, only observational, non-randomized cohort studies can inform clinical practice. Therefore, we performed a retrospective real-world cohort study of patients with advanced HCC treated with sorafenib to investigate its efficacy and safety profile.

2. Materials and methods

This was a retrospective cohort study conducted between January 2016 and June 2018, including 42 patients admitted to the Department of Medical Oncology, Fundeni Clinical Institute, Bucharest. To be included in the study, patients with HCC needed to have been treated with sorafenib for at least two months. Patients received a daily dose of 800 mg of sorafenib, 400 mg (two tablets of 200 mg) taken twice daily, in the morning and in the evening. The treatment was continued for as long as the patients had clinical benefit or until unacceptable toxicity or death. In the case of toxicity, the dose was either reduced to 400 mg/day or stopped. The study was performed in accordance with standard ethical guidelines approved by the local institutional review board and with the Declaration of Helsinki (10).

Individual medical records were reviewed for demographic and clinical information, as all patients gave written informed consent prior to treatment, according to our institutional guidelines. Data on the clinical profile at admission, etiology and stage of the disease (BCLC), liver function (Child-Pugh score), Eastern Cooperative Oncology Group (ECOG) performance status, portal vein thrombosis, lymphadenopathy, the presence of extrahepatic disease at diagnosis, alpha-fetoprotein (AFP) values, and previous treatments were recorded. The primary outcome was overall survival (OS) from the initiation of sorafenib. Secondary outcomes were progression-free survival (PFS), the frequency of specific adverse effects and requirements for dose reduction or drug cessation due to intolerability. Tumor response assessment was performed every 6 months

with CT-scan or MRI and was evaluated according to mRECIST criteria (11). Complete blood count, liver and kidney function tests, coagulation tests and serum AFP were assessed every month. The treatment with sorafenib was continued for patients with clinical or radiological benefit.

Statistical analysis

The Kaplan-Meier method was used to estimate curves corresponding to the average patient follow-up period, progression-free survival, and overall survival. The obtained curves were compared using log-rank tests (Mantel-Cox test) to determine the prognostic factors for longer survival. OS was defined as the time from treatment initiation to death. Patients alive at the time of last follow-up were censored in the OS analysis. PFS was calculated as the time from treatment initiation to the date of disease progression or death from any cause. The patients alive at the time of last follow-up were censored. Univariate analysis was performed for the main known prognostic factors of advanced HCC: age, sex, performance status (ECOG), liver function (Child-Pugh), HCC stage (BCLC), and AFP value.

The following programs were used for data processing and graphical representation of results: Hipocrate Clinic, IBM SPSS 23, and XLSTAT-Biomed 2016. The database was closed for analysis in June 2018. The threshold for statistical significance was 5%. All p-values are two-sided and reported with 95% confidence intervals. The mean follow-up time was 12.9 months (95% CI: 9.8-14.8 months). The Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) was used to evaluate and grade adverse events (AE).

3. Results

Among the 42 patients included in our study, HCC occurred more often in male patients (33 patients – 78.57%), with a mean age at diagnosis of 60.9 years (range 33-78). Regarding the etiology, HCV infection was the most common risk factor that led to the development of HCC (17 patients - 40%), followed by HBV (14 patients - 33.33%), while the rest of the cases (11 patients – 26.2%) were due to HBV + hepatitis D virus (HDV) infection, NASH and toxic hepatitis (see Table 1).

According to the Barcelona Clinic Liver Cancer staging system, most patients (29 patients – 69%) were BCLC stage C. Twenty-eight (66.66%) patients were ECOG 1 at the time of diagnosis. 32 (76.2%) patients were Child-Pugh A. We also found that 18 (42.86%) patients had AFP levels of over 400 ng/ml, 16 (38%) of them had AFP levels of 20–400 ng/ml, and 8 (19%) patients had normal levels of AFP.

At the time of the diagnosis, 16 (38%) patients presented with portal vein thrombosis and 29 (69%) patients presented with extrahepatic disease. The most common site of metastatic spread was the peritoneum (5 patients - 12%), followed by the lung (three patients - 7.14%), bone (two patients - 4.86%) and one (2.38%) patient had adrenal metastases (see Table 1).

Twenty-seven (64%) patients received other treatment prior to sorafenib**.** Nine (21.42%) patients underwent at least one transarterial chemoembolization (TACE) session, eight (19%) patients underwent hepatectomy, four (9.5%) patients received radiofrequency ablation (RFA) and one (2.38%) patient underwent liver transplantation.

Table 1. Clinical characteristics of patients included in the study

Patients and disease characteristics		Number	PERCENTAGE
Gender	Male	33	78.57%
	Female	9	21.42%
Etiology	HCV	17	40.47%
	HBV	14	33.33%

	HBV+HDV NASH	11	26.2%
BCLC Stage	B	13	31%
	C	29	69%
ECOG PS	0-1	28	66.66%
	2	14	33.33%
Child pugh	A	32	76.2%
	B	10	23.8%
AFP LEVEL	<400 ng/ml	24	57.14%
	>400 ng/ml	18	42.86%
Portal vein thrombosis		16	38%
Metastatic sites	peritoneum	5	12%
	lung	3	7.14%
	bone	2	4.76%
	adrenal	1	2.38%

Overall survival

Of the 42 patients, 16 who were alive at the time were censored when the database closed in June 2018. Fourteen were still receiving sorafenib at the time. The median OS for the study group was 11.6 months (95% CI: 9.2-14.1 months) (Figure 1).

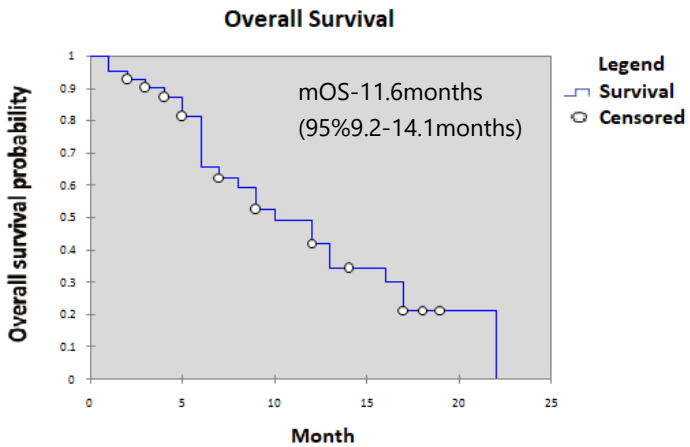


Figure 1. Kaplan Maier Survival Curve for all patients

Univariate analysis showed that reduced survival was associated with 2 ECOG performance status ($p < 0.001$). The median OS of patients with ECOG 1 was 13.8 months (95% CI: 11.3–16.4 months), while the median OS of patients with ECOG 2 was 4.5 months (95% CI: 3.4–5.5 months) (Figure 2).

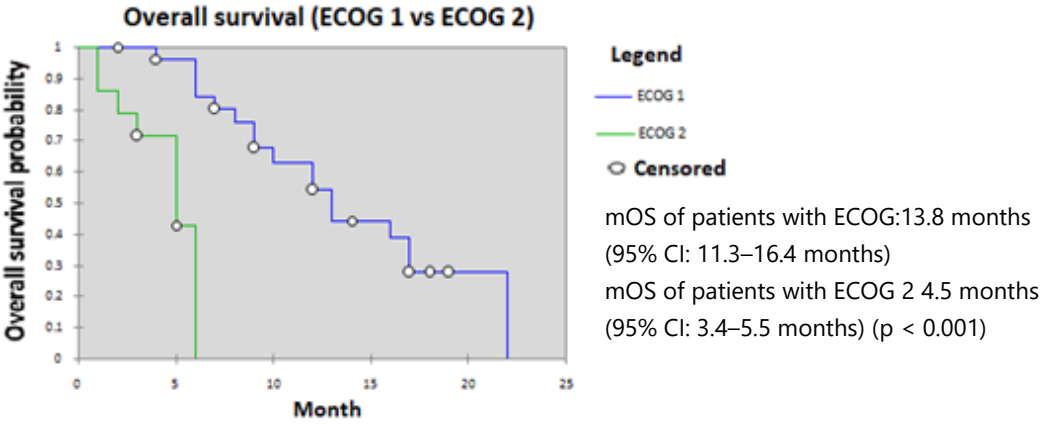


Figure 2. Kaplan Maier Survival Curve; Overall Survival according to ECOG Performance Status.

For patients with HCC and Child-Pugh A liver cirrhosis, the median OS was 12.6 months (95% CI: 10.0-15.2 months). For patients with Child-Pugh B, the median OS decreased to 5.3 months (95% CI: 3.8-6.7 months), but the difference was not statistically significant (p = 0.104) (Figure 3).

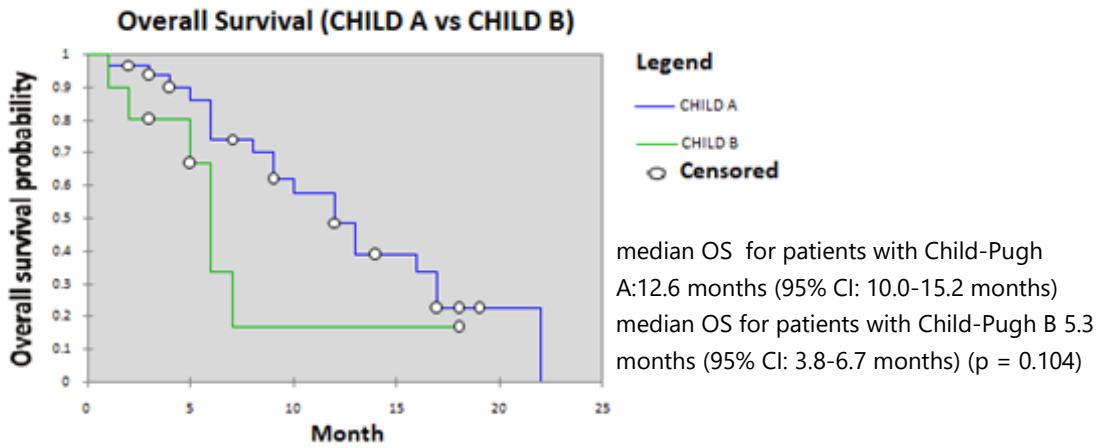


Figure 3. Kaplan Maier Survival Curve Median Overall Survival according to Child-Pugh classification of cirrhosis.

The median OS was calculated according to BCLC stage: the median OS of BCLC B patients was 15.4 months (95% CI: 12.4-19.4 months) and the median OS for BCLC C was 8.8 months (95% CI: 6.7-10.9 months) (Figure 4). Median OS by AFP value was calculated; for patients with AFP < 20 ng/ml, median OS was 8.3 months (95% CI: 4.6-12.0); for patients with AFP levels between 20-400 ng/ml, median OS was 12.3 months (95% CI: 8.9-15.7); and for patients with AFP levels > 400 ng/ml, median OS was 10 months (95% CI: 6.9-13.1). The comparative difference between these variables was not statistically significant.

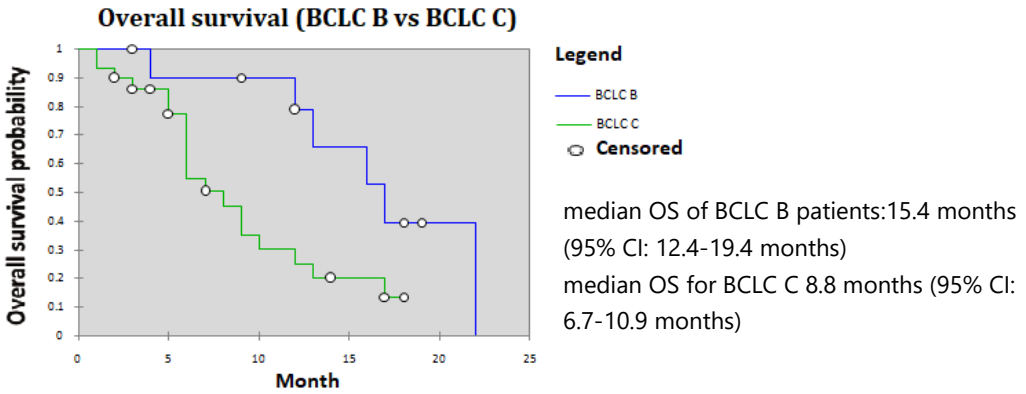


Figure 4. Kaplan Maier Survival Curve Median Overall Survival according to BCLC classification.

The median PFS was 7.7 months (95% CI: 5.8-9.6 months) for the whole study group. Baseline performance status had a effect on PFS. Thus, the median PFS for patients with ECOG 1 was 9.1 months (95% CI: 7.9-11.2 months), while the median PFS for patients with ECOG 2 was 3.9 months (95% CI: 2.9-4.7 months), p<0.001. Child-Pugh score and BCLC stage had no statistically significant impact on PFS for the patients included in the study.

All 42 patients enrolled in the study received an initial dose of 800 mg/day sorafenib, with dose adjustments based on toxicity. Most adverse events occurred within 30 days of beginning sorafenib. Approximately 59% of patients had at least one adverse event and 9% had grade 3–4 adverse events. Drug-related adverse events were experienced by 40% of patients and 7% had grade 3–4 drug-related adverse events. Overall, 23,8% of patients (*n* = 10) experienced serious adverse events, among which only 1 event was drug-related (0.2%). No differences in overall adverse events, serious adverse events or deaths were observed between Child-Pugh A and Child-Pugh B patients. The most common adverse event was fatigue (76%), followed by diarrhea (51%), hypertension (33%), weight loss (30%) and hand-foot skin reaction (14.3%).

Serious adverse events requiring discontinuation of sorafenib were reported in four patients and included diarrhea, uncontrolled arterial hypertension, and hand-foot skin reaction.

4. Discussions

This study aimed to evaluate the effectiveness and safety profile of sorafenib in patients with advanced HCC. The median OS of the whole study group was 11.6 months (95% CI: 9.2-14.1). The patients included in the SHARP trial had a median OS of 10.7 months, followed by the Italian SOFIA study (SOraFenib Italian Assessment) with a median OS of 10.5 months and the Asia-Pacific study with a median OS of 6.5 months (6,7,12). Other studies conducted around the world had the following results: the Egyptian study reported a median OS of 6.25 months, while the median OS in the Danish study was 6.2 months (13,14). The GIDEON study (Global Investigation of therapeutic DEcisions in HCC and Of its treatment with SorafeNib) reported different results between the ethnic and regional groups treated with sorafenib for unresectable HCC (15). Patients from Japan had the longest median OS of 14.7 months (16). The use of sorafenib in our patients with advanced stage HCC is superior compared to other studies regarding the median OS, mainly because sorafenib has been administered to patients with clinical benefit after radiological progression.

According to our results, the median PFS was 7.7 months (95% CI: 5.8-9.6), longer compared to the SHARP trial (4.1 months) and also compared to the Asia-Pacific trial (5.5 months) (6,7). Our data suggested a higher median OS for women (12.6 months) than for men (11.2 months), without finding a statistical

significance (p=0.533). However, CT or MRI evaluated treatment response to sorafenib for the patients included in our study every 6 months, and this could be a possible explanation for the longer PFS.

According to the BCLC staging system, most patients (29/42) were BCLC stage C, while the remaining 13 were BCLC stage. The median OS of patients with BCLC stage B was higher than the median OS of patients with BCLC stage C (15.4 months vs. 8.8 months), but the difference was not statistically significant. The median PFS was 10.7 months (95% CI: 7.2–13.2) for BCLC stage B and 6.2 months (95% CI: 4.1–8.4) for BCLC stage C HCC.

Median OS of patients with ECOG 1 was significantly ($p < 0.001$) higher than patients with ECOG 2 (13.8 months vs. 4.5 months). In the Asia-Pacific study, patients with ECOG 1 and ECOG 2 had a median OS of 6.1 months (6). In the Egyptian study, median PFS was 7 months in patients with ECOG 1 and 3 months in patients with ECOG 2 (13). In our study, median PFS was 9.1 months (95% CI: 7.9-11.2) for ECOG 1 and 3.9 months (95% CI: 2.9-4.7) for ECOG 2 ($p = 0.001$). ECOG performance status reflects how the disease affects patients' daily lives, thus being a strong prognostic factor.

Most patients in our study (32 patients) were Child-Pugh A. The median OS in Child-Pugh A patients was higher than in Child-Pugh B patients (12.6 months vs. 5.3 months), but the difference did not reach statistical significance. Patients enrolled in the Egyptian study were similar, with a median OS of 12 months in patients with Child-Pugh A and a median OS of 5.2 months in patients with Child-Pugh B (13). According to our results, the median PFS was 8.3 months (95% CI: 6.2-10.5) for Child-Pugh A patients and four months (95% CI: 3.1-4.9) for Child-Pugh B patients.

Interestingly, patients with AFP levels < 20 ng/ml had a median OS of 8.3 months (95% CI: 4.6-12), which was lower than those with AFP between 20-400 ng/ml who showed a median OS of 12.3 months (95% CI: 8.9-15.7). Also, 18 patients had AFP levels > 400 ng/ml and they had a better OS (10 months, 95% CI: 6.9-13.1) than those with normal AFP levels, but without statistical significance ($p = 0.257$). The median duration of sorafenib treatment in our study was 8.2 months (95% CI: 6.9-10.4 months). Some patients received sorafenib beyond radiological progression, which could explain why OS is higher than PFS in our study. Apostolodis et al. published similar results, showing that patients who continue sorafenib for three months beyond progression have higher OS compared to patients that discontinue sorafenib in under three months or immediately after radiological progression (17).

Therefore, we can say that sorafenib is a treatment that brings a clinical benefit to Romanian patients if it is administered to patients with a good performance status (ECOG 0,1) and with compensated liver function (Child-Pugh class A). The outcomes of patients with impaired performance status and impaired liver function are measurably worse.The use of sorafenib in patients with advanced stage HCC has been shown to be superior in terms of overall survival when compared to other studies (Sharp: 10.7 months; Asia-Pacific study: 6.5 months; Egyptian study: 6.25 months) (6,7,13). This can be explained by the fact that sorafenib was administered to patients after radiologic confirmation of progressive disease, based only on clinical benefit and the dose was reduced or the treatment was discontinued if unacceptable toxicity occurred.

Several limitations of the current study must be acknowledged. This was a retrospective single-center study with a small sample size. Tumor response to sorafenib therapy was evaluated after at least 5 months of treatment, which could explain the longer median OS and PFS of patients included in the study compared to sorafenib registration trials.

5. Conclusions

Hepatocellular carcinoma continues to be a significant public health problem in Romania. Its incidence and mortality rate continue to increase, and the disease has significant socio-economic consequences. This retrospective single-center study confirmed the benefit of

sorafenib in treatment of advanced HCC, particularly in patients with well-preserved liver function and performance status. The median OS of the entire study group was 11.6 months, which was significantly longer than the median OS in phase III trials. Patients with ECOG 1, Child-Pugh A, or BCLC stage B HCC had an improved survival rate.

Abbreviations:

AFP - alpha-fetoprotein
BCLC - Barcelona Clinic Liver Cancer
ECOG - Eastern Cooperative Oncology Group
CT - Computer Tomography
HBV - hepatitis B virus
HCV - hepatitis C virus
HDV - hepatitis D virus
HCC - Hepatocellular Carcinoma
NASH - nonalcoholic steatohepatitis
MR - magnetic resonance imaging
OS - overall survival
PDGFR - platelet-derived growth factor receptor
PFS - progression-free survival
RFA - radiofrequency ablation
RECIST - Response Evaluation Criteria in Solid Tumors
TACE - transarterial chemoembolization
VEGFR - vascular endothelial growth factor receptor
WHO - World Health Organization

Statements:

Authors' contributions: CSG: study design, research, wrote the paper, conceived the analysis, statistical analysis SD: study design, review of the manuscript and consent for publication: LMN, MM, LCA, GC review of the manuscript. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Conflict of interest: All authors declare having no competing interests associated with this publication.

Ethics approval: Study approved by the local IRB.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

Patients' consent: Study included retrospective data and the patients` information was de-identified.

References:

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.

2. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of Hepatocellular Carcinoma. Vol. 73, Hepatology. 2021. p. 4–13.

3. Schumacher PA, Powell JJ, MacNeill AJ, Buczkowski AK, Erb SR, Ho SG, et al. Multimodal therapy for hepatocellular carcinoma: A complementary approach to liver transplantation. Ann Hepatol. 2010;9(1).

4. Zhu YJ, Zheng B, Wang HY, Chen L. New knowledge of the mechanisms of sorafenib resistance in liver cancer. Vol. 38, Acta Pharmacologica Sinica. 2017. p. 614–22.

5. Gutzmer R, Wollenberg A, Ugurel S, Homey B, Ganser A, Kapp A. Cutaneous side effects of new antitumor drugs: clinical features and management. Dtsch Arztebl Int. 2012 Feb;109(8):133–40.

6. Cheng A-L, Kang Y-K, Chen Z, Tsao C-J, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009 Jan;10(1):25–34

7. Rimassa L, Santoro A. Sorafenib therapy in advanced hepatocellular carcinoma: The SHARP trial. Expert Rev Anticancer Ther. 2009;9(6):739–45.

8. Koulouris A, Tsagkaris C, Spyrou V, Pappa E, Troullinou A, Nikolaou M. Hepatocellular Carcinoma: An Overview of the Changing Landscape of Treatment Options. J Hepatocell Carcinoma. 2021;Volume 8(8):387–401.

9. Hanzel J, Kosir Bozic T, Stabuc B, Jansa R. Sorafenib for the treatment of hepatocellular carcinoma: a single-centre real-world study. Radiol Oncol. 2020 May;54(2):233–6.

10. GANDEVIA B, TOVELL A. DECLARATION OF HELSINKI. Med J Aust. 1964;2.

11. Vincenzi B, Di Maio M, Silletta M, D'Onofrio L, Spoto C, Piccirillo MC, et al. Prognostic relevance of objective response according to EASL criteria and mRECIST criteria in hepatocellular carcinoma patients treated with loco-regional therapies: A literature-based meta-analysis. PLoS One. 2015;10(7).

12. Iavarone M, Cabibbo G, Piscaglia F, Zavaglia C, Grieco A, Villa E, et al. Field-practice study of sorafenib therapy for hepatocellular carcinoma: a prospective multicenter study in Italy. Hepatology. 2011 Dec;54(6):2055–63.

13. Abdel-Rahman O, Abdelwahab M, Shaker M, Abdelwahab S, Elbassiony M, Ellithy M. Sorafenib for Egyptian patients with advanced hepatocellular carcinoma; single center experience. J Egypt Natl Canc Inst. 2014;26(1):9–13.

14. Køstner AH, Sorensen M, Olesen RK, Grønbæk H, Lassen U, Ladekarl M. Sorafenib in advanced hepatocellular carcinoma: A nationwide retrospective study of efficacy and tolerability. Sci World J. 2013;2013:1–6.

15. Lencioni R, Kudo M, Ye S-L, Bronowicki J-P, Chen X-P, Dagher L, et al. GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib): second interim analysis. Int J Clin Pract. 2014 May;68(5):609–17.

16. Nishikawa, Hiroki, et al. "Comparison of standard-dose and half-dose sorafenib therapy on clinical outcome in patients with unresectable hepatocellular carcinoma in field practice: A propensity score matching analysis." International journal of oncology 45.6 (2014): 2295-2302.

17. Apostolidis L, Pfeiffenberger J, Gotthardt D, Radeleff B, Mehrabi A, Schemmer P, et al. Survival of Hepatocellular Carcinoma Patients Treated with Sorafenib beyond Progression. Gastrointest Tumors. 2018;5(1–2).

JMRO

Journal of Medical and Radiation Oncology

Journal homepage: www.jmedradonc.org

Sequential Volumetric Modulated Arc Therapy (VMAT) Boost in Hybrid Plan With Tangential Beams for Whole Breast Treatment: a Dosimetric Study

Antonio Piras[1], Luca Boldrini[2], Andrea D'Aviero[3]*, Antonella Sanfratello[4], Sebastiano Menna[2], Mariangela Massaccesi[2], Massimiliano Spada[5], Gianfranco Pernice[5], Tommaso Angileri[6], Antonino Daidone[1]

[1] UO Radioterapia Oncologica, Villa Santa Teresa, Bagheria, Palermo

[2] UOC Radioterapia Oncologica - Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Dipartimento di Diagnostica per immagini, Radioterapia Oncologica ed Ematologia, Roma

[3] Radiation Oncology, Mater Olbia Hospital, Olbia, Sassari, Italy

[4] Università degli Studi di Palermo, Radioterapia Oncologica, Palermo

[5] UO Oncologia, Fondazione Istituto G. Giglio, Cefalù, Palermo

[6] UO Radiologia, Villa Santa Teresa, Bagheria, Palermo

Corresponding author: Andrea D'Aviero; **e-mail**: andrea.daviero@materolbia.com

Origininal Research

Abstract

Purpose: Whole breast radiation therapy (WBRT) with a boost to the tumor bed following conservative primary surgery in women with breast cancer (BC) plays a central role in reducing local recurrences and mortality. Volumetric modulated arc therapy (VMAT) technique has been shown to allow better dose conformation with low dose levels to organs at risk (OARs), compared to static fields three-dimensional Conformal Radiotherapy (3D-CRT). The aim of this study was to evaluate the feasibility and dosimetric advantages of sequential boost (SB), administered with VMAT technique in hybrid plans with tangential beams for whole breast treatment.

Material and methods: BC patients undergoing adjuvant RT from June to October 2020 were selected. ESTRO guidelines for the Clinical Target Volume (CTV) delineation were used. Total delivered dose was 60-66 Gy; 50 Gy in 2 Gy daily fractions for whole breast and 10-16 in 2 Gy daily fractions Gy to tumor bed was 10-16 Gy in 2 Gy daily fractions.

Results: The analysis included 31 patients with BC treated with adjuvant RT following conservative surgery. Hybrid treatment plans characterized by a 3D-CRT plan using tangential mediolateral and lateromedial fields for the irradiation of the whole breast Planning Target Volume (PTV) and a sequential VMAT plan with 2 coplanar arches for boost PTV irradiation were generated. Dosimetric analysis resulted in homogeneous target volumes coverage and OARs

https://doi.org/10.53011/JMRO.2022.01.04
2784 – 0131/Copyright 2022 The Author(s).

constraints compliance. As regarding to organs at risks (OARs), contralateral breast, ipsi- and contralateral lung and heart constraints values were analysed.

Conclusions: In the frame BC RT, this dosimetric study showed that hybrid plans performed with 3D-CRT and VMAT techniques are feasible in terms of dosimetric outcomes.

Keywords: *Breast Cancer, Radiotherapy, Hybrid plans, VMAT, 3D-CRT*

Introduction

Breast conservative surgery followed by whole breast radiation therapy (WBRT) and a boost to the tumor bed is the treatment of choice for most patients with stages I–II breast cancer (BC) (1–3).

Breast radiotherapy (RT) has been historically performed by two tangential fields for a total dose of about 50 Gy with a conventional fractionation of 1.8-2 Gy (4). More recent evidence have demonstrated the non-inferiority of hypofractionated RT also showing a reduction in acute toxicity (5–9).

Breast conservative approaches have increased significantly in the last decades and techniques have improved with greater awareness of the impact of radiation on the heart (10).

The tumor bed boost can be performed in different modalities, electrons beam radiotherapy, particles RT, photons beam RT or brachytherapy (BT). Electrons beam RT and photons beam RT delivered in sequential boost (SB) have been shown to be the most common modalities (11,12).

Even though particles RT and photons beam RT seem to guarantee better planning solutions, no randomized trials have been designed to identify the best modality to use (13,14).

In recent years, static fields three-dimensional Conformal Radiotherapy (3D-CRT) modality has been replaced by Intensity-Modulated Radiation Therapy (IMRT) modality assuring more conforming doses and volumes. Experience have also showed that IMRT could also provide a minimization of unwanted radiation dose inhomogeneity in the breast leading to late adverse effects reduction (15,16).

Volumetric modulated arc therapy (VMAT) technique is preferred to conventional direct electron in tumor bed boost both for better conformation of the dose and for lung sparing (17).

Electrons should be reserved to very superficially located tumor bed without contact with the thoracic wall (18).

To our knowledge, in literature no studies have analyzed a hybrid treatment with static tangential fields for WBRT and with the use of VMAT technique for the sequential boost.

The aim of this study is to demonstrate the feasibility and dosimetric advantages of SB delivered with VMAT technique in hybrid plans with tangential beams for whole breast treatment.

Material and methods

Patients characteristics

Thirty-one patients from a single institution who received RT following conservative surgery for early BC from June to October 2020 were retrospectively enrolled. Patients enrolled signed a consent for data collection according to the study design requirements and also to department regulation.

Patients had stage I disease according to the 7th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging system (19).

In this study 12 left-sided and 19 right-sided tumors were evaluated.

A heterogeneous patient population was considered for analysis with large or small breast volume and deeply or superficially located tumors.

The boost regions were sixteen in upper outer quadrant (UOQ), two in upper-lower inner quadrants (UIQ – LIQ), two in lower outer quadrant (LOQ), eleven in central quadrant (CQ).

Patients characteristics are reported in table 1.

Table 1 - *Patients characteristics*

Patient	Side	Quadrant	Gy/fraction Whole breast	Total dose Whole breast	Gy/fraction Tumoral bed	Total dose Tumoral bed
1	R	UOQ	2	50	2	10
2	R	LOQ	2	50	2	10
3	L	UOQ	2	50	2	10
4	R	CQ	2	50	2	10
5	R	LOQ	2	50	2	10
6	R	UOQ	2	50	2	16
7	L	CQ	2	50	2	10
8	L	CQ	2	50	2	16
9	R	CQ	2	50	2	10
10	L	UOQ	2	50	2	10
11	R	CQ	2	50	2	10
12	R	UIQ-LIQ	2	50	2	10
13	L	CQ	2	50	2	10
14	R	UOQ	2	50	2	16
15	L	UOQ	2	50	2	10
16	R	UOQ	2	50	2	10
17	R	UOQ	2	50	2	10
18	R	UIQ-LIQ	2	50	2	10
19	R	UOQ	2	50	2	10
20	R	UOQ	2	50	2	10
21	R	UOQ	2	50	2	10
22	L	UOQ	2	50	2	10
23	L	QC	2	50	2	10
24	L	UOQ	2	50	2	10
25	L	UOQ	2	50	2	10
26	R	UOQ	2	50	2	10
27	R	UOQ	2	50	2	10
28	R	CQ	2	50	2	10
29	L	CQ	2	50	2	10
30	R	CQ	2	50	2	10
31	L	CQ	2	50	2	10

R: right; L: left; UOQ: upper outer quadrant; LOQ: lower outer quadrant. UIQ: upper inner quadrant; LIQ: lower inner quadrant; CQ: central quadrant;

Contouring

The patients underwent a 2.5-mm slice thickness, free-breathing computed tomography (CT) scan in supine position on breast board (C-qual) with both arms raised above the head.

The clinical target volume of whole breast (CTV_{breast}) was contoured according to European Society for Radiotherapy and Oncology (ESTRO) guidelines (20).

The CTV_{boost} was defined as the tumor bed identified through the study of pre-operative mammography and/or MRI images and the visualization of the surgical alteration, with the help of a metal marker on the scar; any seromas near the tumor bed were included.

The PTV_{breast} and PTV_{boost} were created by adding an isotropic 5 mm margin expansion to CTV_{breast} and CTV_{boost} respectively.

The PTVs were cropped to 5 mm from the body as Italian guideline recommendation (1).

The organs at risk (heart, ipsilateral lung, contralateral lung and lungs) were delineated according to National guidelines (1).

Planning

31 hybrid treatment plans were generated characterized by a 3D-CRT plan using tangential mediolateral and lateromedial fields for the irradiation of the PTV_{breast} and a sequential VMAT plan with 2 coplanar arches for PTV_{boost} irradiation with an amplitude of 120° (240°-40° for right breast, 320°- 120° for left breast).

All treatment plans were calculated using the Pinnacle3 vers.16.02 from Philips, collapsed cone algorithm and 3x3x2.5 mm calculation grid and were optimized for Elekta Synergy® linear accelerator equipped with an 80-leafs multi-lamellar collimator.

The dose prescribed to the whole breast was 50 Gy in 2 Gy daily fractions according to internal department regulamentation. The dose to the tumor bed was 10-16 Gy in 2 Gy daily fractions, higher boost dose was prescribed for patients with close margins status at pathological examination. The total delivered dose was 60-66 Gy.

The target volume and prescription dose were defined according Report 50, 62 and 83 recommendations of the International Commission on Radiation Units and Measurements (ICRU) (21–23).

Both plans aimed to PTV V95% and CTV 98% higher than 95% of the prescribed dose, and also to PTV V107% inferior to 5% and PTV Dmax not exceeding 110%.

The conformity index ($CI_{95\%}$) was calculated as

$$CI = \frac{TV_{RI}}{TV} \cdot \frac{TV_{RI}}{V_{RI}}$$

where TV_{RI} represents the target volume covered by the reference isodose (95% of the prescription dose); TV is the target volume, V_{RI} is the volume of the reference isodose. The value of CI ranges from 0-1, with a value closer to 1 indicating better conformity of the dose to the PTV (24).

The dose constraints considered for Organs at risk (OARs) were:

- Heart V10Gy < 10%, V40Gy < 4% and Dmean < 3 Gy
- Ipsilateral lung Dmean < 18 Gy and V20Gy < 25%
- Contralateral lung Dmax < 5 Gy
- Bilateral lungs V5Gy < 60%
- Contralateral breast Dmax < 5 Gy and V10 Gy < 5%. (25–27)

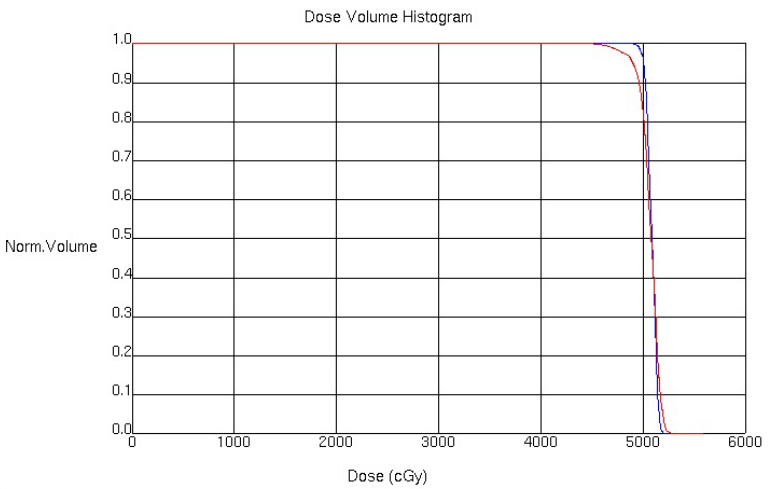
Plan evaluation

The dosimetric data of the individual and the sum plans considered were:

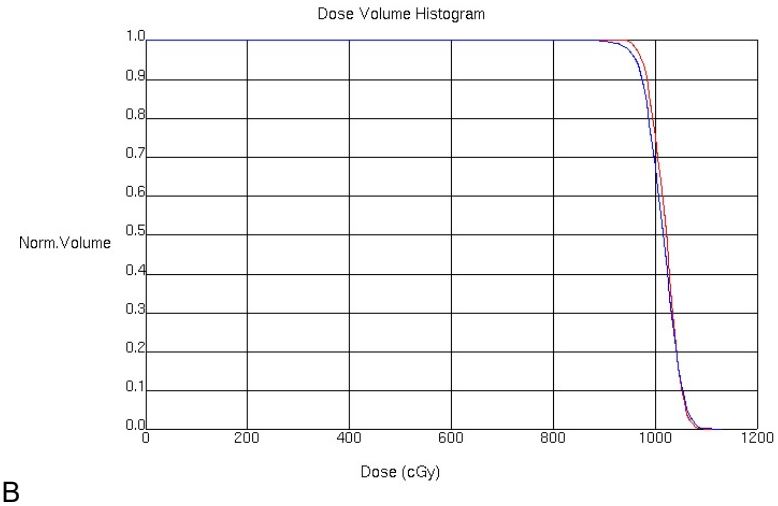
- CTV boost bed V95% and V107%
- PTV boost bed V95%, V107% and $CI_{95\%}$
- Ipsilateral lung mean dose and V20Gy
- Contralateral lung max dose and mean dose
- Bilateral lungs V5Gy
- Heart V20Gy, V40Gy and mean dose
- Contralateral breast max dose and V10Gy

3. Results

Plan evaluation resulted in homogeneous dosimetric values for target coverage as Mean PTV boost V95% resulted in 98,2% ± 1,8 DS with a mean PTV boost CI 95% result of 1,0 ± 0,0 DS. Coverage of both PTV_{breast} and PTV_{boost} are shown in Figure 1 and 2.



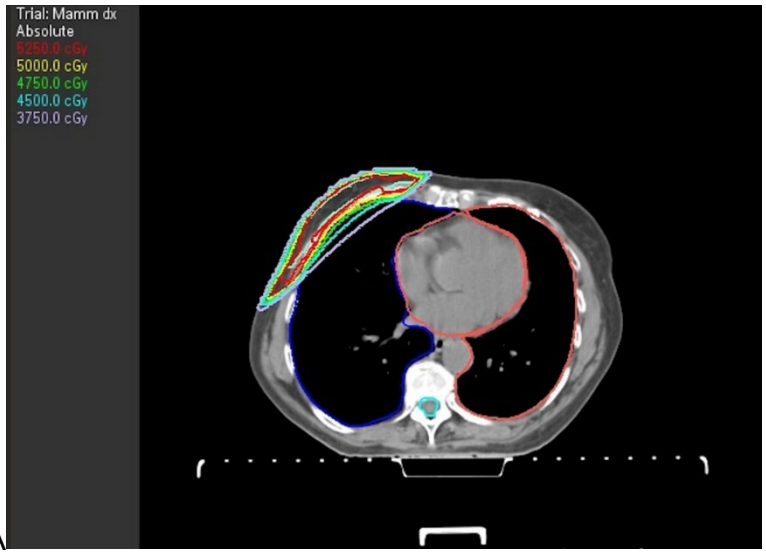
A



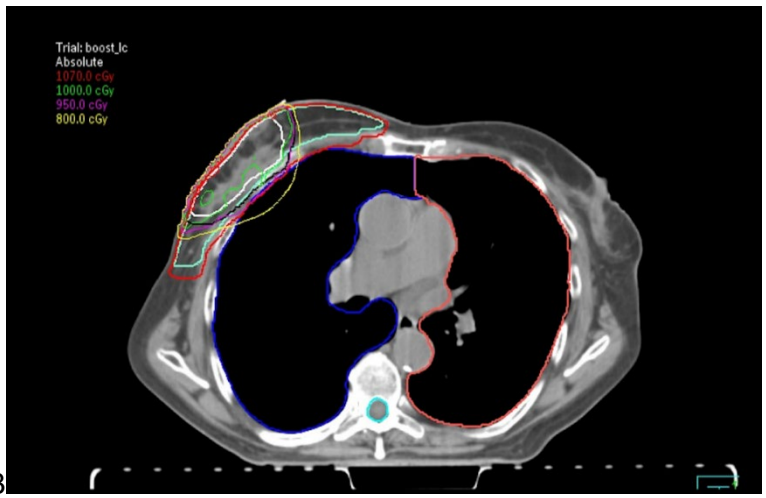
B

PTV: planning target volume

Figure 1 – Dose Volumes Histograms for PTV_{breast} (A) and PTV_{boost} (B)



A



B

PTV: planning target volume

Figure 2 – Dose coverage for PTVbreast (A) and PTVboost (B)

Heart constraints were respected as mean heart V20 Gy resulted in 1,4 Gy ± 2,5 DS and 1,5 Gy ± 2,7 DS in WBRT plans and boost plans sum. Also constraints for the other OARs were respected.

Table 2 and 3 resume data of target coverage and OARs doses in both WBRT and boost plans sum.

Table 2 - Target coverage values

	CTV boost V95%	**CTV boost V107%**	**PTV boost V95%**	**PTV boost V107%**	**PTV boost V110%**	**PTV boost Dmax**	**PTV CI 95%**
MEAN	99.8	1.3	98.2	1.4	0.0	10.4	1.0
ST. DEV	*0.3*	*1.5*	*1.8*	*1.6*	*0.1*	*2.7*	*0.0*

CTV: Clinical Target Volume; PTV: Planning Target Volume; CI: Conformity Index; ST. DEV: Standard Deviation

Table 3 - OARs dose constraints values

	Heart V20Gy Boost	**Heart V20Gy WBRT**	**Heart V20Gy Plan Sum**	**Heart V40Gy Boost**	**Heart V40Gy WBRT**	**Heart V40Gy Plan Sum**	**Heart Dmean Boost**	**Heart Dmean WBRT**	**Heart Dmean Plan Sum**
MEAN	0.0	1.4	1.5	0.0	0.6	0.7	1.0	1.7	2.7
ST. DEV	*0.0*	*2.5*	*2.7*	*0.0*	*1.1*	*1.3*	*0.7*	*1.4*	*1.6*

	Contralateral Breast Dmax Boost	**Contralateral Breast Dmax WBRT**	**Contralateral Breast Dmax Plan Sum**	**Contralateral Breast V10Gy Boost**	**Contralateral Breast V10Gy WBRT**	**Contralateral Breast V10Gy Plan Sum**
MEAN	1.2	2.8	3.8	0.0	0.2	0.3
ST. DEV	*0.5*	*1.0*	*1.0*	*0.0*	*0.6*	*0.8*

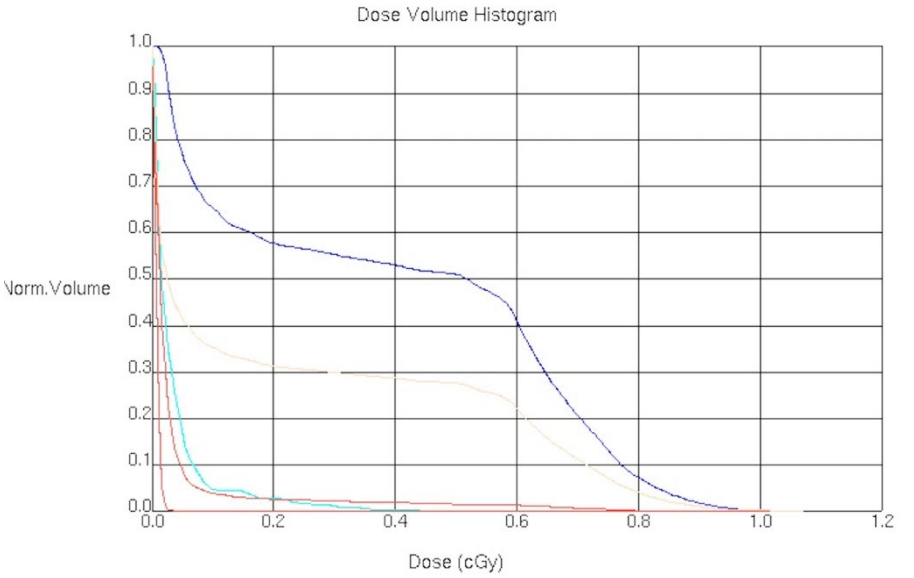
	Ipsilateral Lung Dmean Boost	***Ipsilateral Lung Dmean WBRT***	***Ipsilateral Lung Dmean Plan Sum***	***Ipsilateral lung V20Gy Boost***	***Ipsilateral Lung V20Gy WBRT***	***Ipsilateral Lung V20Gy Plan Sum***
MEAN	*1.3*	*8.1*	*9.4*	*0.0*	*13.7*	*14.8*
ST. DEV	*0.6*	*3.3*	*3.2*	*0.0*	*5.0*	*5.3*

	Contralateral Lung Dmean Boost	*Contralateral Lung Dmean WBRT*	*Contralateral Lung Dmean Plan Sum*	*Contralateral Lung Dmax Boost*	*Contralateral Lung Dmax WBRT*	*Contralateral Lung Dmax Plan Sum*
MEAN	*0.4*	*0.3*	*0.7*	*1.9*	*2.4*	*3.7*
ST. DEV	*0.1*	*0.3*	*0.3*	*0.7*	*0.9*	*1.1*

	Lungs V5Gy Boost	**Lungs V5Gy WBRT**	**Lungs V5Gy Plan Sum**
MEAN	2.4	13.7	17.8
ST. DEV	*2.1*	*5.0*	*6.2*

ST. DEV: Standard Deviation; WBRT: Whole Breast Radiotherapy

No statistically significant differences in Heart Dmean of PTV boost (p=0,14) were shown. Dose volume histograms for OARs ais shown Figure 3.



OARs: Organs at risk

Figure 3 – Dose Volumes Histograms for OARs

4. Discussion

This study analyzes the dosimetric data of adjuvant radiation treatment plans in patients with early stage BC, using hybrid plans delivered through a 3D-CRT plan for WBRT and a sequential VMAT plan for tumor bed boost.

The use of hybrid plans could allow us to improve the dose homogeneity without exceeding the low doses rates typical of WBRTs performed entirely with the IMRT / VMAT technique.

In addition, the delivery of the single boost with the VMAT technique proved to be really simple and fast, with excellent visualization

and reproducibility of the target through daily cone beam computed tomography (CBCT).

A recent experience showed that whole breast IMRT and Hypofractionated VMAT RT are feasible and well tolerated in elderly patients affected by early-stage BC, also showing lower risks of acute and late RT-related side effects (28).

Several experiences have been published regarding RT treatments with IMRT-VMAT technique with simultaneous integrated boost (SIB) and Accelerated Partial Breast Irradiation (APBI) (28–31; 47). Further studies also compared sequential boost with simultaneous boost.

A significant reduction in the severity of acute radiation dermatitis in IMRT-SIB RT compared to 3D-CRT-SB was shown (32).

Preliminary data from the prospective IMRT-MC2 trial, reported a non-inferiority of IMRT-SIB versus 3D-CRT sequential boost with respect to cosmesis and LC at 2 years of follow up (33).

IMRT planning also has been shown to provide higher dose conformity and to assure shorter treatment duration, even though with a slightly higher planning maximum and increased lung doses (34).

Other experiences showed a significantly reduced surface dose with IMRT compared to 3D-CRT, in the adjuvant treatment of BC (35).

However, many authors have shown tangential fields RT approach delivered with modern techniques such as IMRT and tomotherapy could be an optimal modality especially for minimizing organs at risk (OAR) low-doses. Nissen et al have demonstrated as deep inspiration breath hold (DIBH) in conjunction with tangential-field, forward-planned IMRT treatment plans can lead to a significant reduction in heart and lung dose while optimizing PTV coverage (36). Other experience showed as tangential fields tomotherapy could result in better dose coverage and OARs constraints compliance compared to other RT modalities (37,38).

A recent experience from Joseph et al, recently showed that IMRT SIB does not seem to have any dosimetric advantage compared to field-in-field 3D-CRT (39). Significantly higher doses to contralateral lung and heart and radiation exposure in terms of Monitor Units were also shown in IMRT SIB treatments (39).

Limited benefits of IMRT have been shown in specific patients subsets, mainly in treatments with large boost planning tumor volume (PTV) and an overlap between heart and breast PTV (40).

Several authors have proposed hybrid plans with SIB to take advantages of both 3D technique and IMRT(41,42). Onal et al demonstrated that the D2, D98, and V107 values for PTV_{breast} and PTV_{boost}, and Homogeneity Index of PTV_{breast} with VMAT technology were higher with SB technique compared to the SIB technique (43).

In the frame of dosimetric analysis, an excellent target coverage and dose homogeneity is shown with mean values of PTV boost CI 95% 1.0 and media of CTV boost V95% 99.8%. Mean PTV boost V107% is always less than 5% except in 1 case where it is 5.1%.PTV boost V110% is always less than 1% and almost always is 0%. This high homogeneity of dose distribution is typical of IMRT / VMAT techniques.

As regarding to OARs, the dosimetric data show that the dose contribution of the boost plan is minimal and does not lead to large variations in the costraints used in clinical practice for treatment plan approvement.

In particular the difference of the heart V20 values between WBRT performed by 3D-CRT technique alone and the plan sum, is always less than 0.5% exception a case that is 1.4%; in most cases the difference is 0%.

Given the latest evidence in the article by Killander et al (26), where no correlation was found between cardiac toxicity and Dmean value inferior to 4 Gy, we have verified that the VMAT boost low doses did not go to affect the increase of this constraint.

We performed a subset analysis of patients with left BC and found no statistically significant differences between right and left side. The mean value of Heart Dmean was 1.0 Gy ± 0.7 SD and allowed not to exceed 3-4 Gy in the plan sum. Authors are aware of the limitations of this study such as the small simple size and the limited number of patients with internal quadrants for whom hearth doses could be increased.

In literature there are no studies investigating the use of hybrid plans with 3D-CRT plan with tangential fields for WBRT and with VMAT / IMRT plan for boosting the tumor bed. Balaji et al demonstated the feasibility of flattening filter-free (FFF) photon beams in hybrid volumetric modulated arc therapy (23). (41).

However, we have found studies that support the use of the VMAT technique for the boost (17,18). Most of the recent literature regarding BC tumor bed boost focuses on SIB studies in full IMRT/VMAT plans. (30,32,33,40,43–46). But some studies suggest that the low doses given by many fractions in IMRT / VMAT may not justify the use of this technique for the entire treatment (34,39).

5. Conclusion

This study aimed to demonstrate the very low impact of boost with VMAT technique on constraints and low doses, to suggest the use of hybrid plans that can avoid the low doses of many fractions with IMRT / VMAT technique but exploit their potential in few fractions of the boost.

Comparative dosimetric studies on this hybrid technique applied in different modalities of treatment and large-scale studies to evaluate clinical outcomes should be designed to address the potential benefit of hybrid treatments.

Abbreviations:

WBRT - whole breast radiation therapy
BC - breast cancer
VMAT - volumetric modulated arc therapy
OARs - organs at risk
3D-CRT - three-dimensional Conformal Radiotherapy
SB - sequential boost
CTV - clinical target volume
PTV - planning tumor volume
RT – radiotherapy
BT – brachytherapy
IMRT - intensity-modulated radiation therapy
AJCC - American Joint Committee on Cancer
UICC - Union for International Cancer Control
UOQ - upper outer quadrant
UIQ – LIQ - lower inner quadrants
CQ - central quadrant
CT - computed tomography
ESTRO - European Society for Radiotherapy and Oncology
ICRU - International Commission on Radiation Units and Measurements
CI - conformity index
CBCT - cone beam computed tomography
SIB - simultaneous integrated boost
APBI - accelerated partial breast irradiation
DIBH - deep inspiration breath hold

Statements:

Authors' contribution - AP: Conceptualization, Writing - Review & Editing; LB: Conceptualization, Supervision; A D'A: Writing - Original Draft, Writing - Review & Editing; AS: Investigation, Data Curation; SM: Investigation, Data Curation; MM: Writing - Review & Editing Supervisio; MS: Writing - Review & Editing; GP: Writing - Review & Editing; TA: Writing - Review & Editing; AD: Supervision.

Funding - This research received no external funding.
Conflicts of Interest - No actual or potential conflicts of interest exist regarding this article.
Data Availability Statement - The data presented in this study are available on request from the corresponding author.
Ethics approval - The study was conducted according to the guidelines of the declaration of Helsinki. Patients enrolled signed a consent for data collection according to the study design requirements and also to department regulation.
Aknowlegments - The Authors are grateful to Dr. Diepriye Charles-Davies for the linguistic revision of this manuscript

References

1. Gregucci F, Fozza A, Falivene S, Smaniotto D, Morra A, Daidone A, et al. Present clinical practice of breast cancer radiotherapy in Italy: a nationwide survey by the Italian Society of Radiotherapy and Clinical Oncology (AIRO) Breast Group. Radiol Med (Torino) 2020;125:674–82. https://doi.org/10.1007/s11547-020-01147-5.

2. Sedlmayer F, Sautter-Bihl M-L, Budach W, Dunst J, Fastner G, Feyer P, et al. DEGRO practical guidelines: radiotherapy of breast cancer I: radiotherapy following breast conserving therapy for invasive breast cancer. Strahlenther Onkol Organ Dtsch Rontgengesellschaft Al 2013;189:825–33. https://doi.org/10.1007/s00066-013-0437-8.

3. Smith BD, Bellon JR, Blitzblau R, Freedman G, Haffty B, Hahn C, et al. Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Pract Radiat Oncol 2018;8:145–52. https://doi.org/10.1016/j.prro.2018.01.012.

4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, Taylor C, Arriagada R, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet Lond Engl 2011;378:1707–16. https://doi.org/10.1016/S0140-6736(11)61629-2.

5. Valle LF, Agarwal S, Bickel KE, Herchek HA, Nalepinski DC, Kapadia NS. Hypofractionated whole breast radiotherapy in breast conservation for early-stage breast cancer: a systematic review and meta-analysis of randomized trials. Breast Cancer Res Treat 2017;162:409–17. https://doi.org/10.1007/s10549-017-4118-7.

6. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 2013;14:1086–94. https://doi.org/10.1016/S1470-2045(13)70386-3.

7. START Trialists' Group, Bentzen SM, Agrawal RK, Aird EGA, Barrett JM, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Lond Engl 2008;371:1098–107. https://doi.org/10.1016/S0140-6736(08)60348-7.

8. Whelan TJ, Pignol J-P, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362:513–20. https://doi.org/10.1056/NEJMoa0906260.

9. Offersen BV, Alsner J, Nielsen HM, Jakobsen EH, Nielsen MH, Krause M, et al. Hypofractionated Versus Standard Fractionated Radiotherapy in Patients With Early Breast Cancer or Ductal Carcinoma In Situ in a Randomized Phase III Trial: The DBCG HYPO Trial. J Clin Oncol Off J Am Soc Clin Oncol 2020;38:3615–25. https://doi.org/10.1200/JCO.20.01363.

10. Boyages J, Baker L. Evolution of radiotherapy techniques in breast conservation treatment. Gland Surg 2018;7:576–95. https://doi.org/10.21037/gs.2018.11.10.

11. Jalali R, Singh S, Budrukkar A. Techniques of tumour bed boost irradiation in breast conserving therapy: current evidence and suggested guidelines. Acta Oncol Stockh Swed 2007;46:879–92. https://doi.org/10.1080/02841860701441798.

12. Kindts I, Verhoeven K, Laenen A, Christiaens M, Janssen H, Van der Vorst A, et al. A comparison of a brachytherapy and an external beam radiotherapy boost in breast-conserving therapy for breast cancer: local and any recurrences. Strahlenther Onkol Organ Dtsch Rontgengesellschaft Al 2019;195:310–7. https://doi.org/10.1007/s00066-018-1413-0.

13. Toscas JI, Linero D, Rubio I, Hidalgo A, Arnalte R, Escudé L, et al. Boosting the tumor bed from deep-seated tumors in early-stage breast cancer: a planning study between electron, photon, and proton beams. Radiother Oncol J Eur Soc Ther Radiol Oncol 2010;96:192–8. https://doi.org/10.1016/j.radonc.2010.05.007.

14. Aghili M, Barzegartahamtan M, Alikhassi A, Mohammadpour R. Investigation of electron boost radiotherapy in patients with breast cancer: Is a direct electron field optimal? Cancer Radiother J Soc Francaise Radiother Oncol 2018;22:52–6. https://doi.org/10.1016/j.canrad.2017.08.109.

15. Donovan E, Bleakley N, Denholm E, Evans P, Gothard L, Hanson J, et al. Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. Radiother Oncol J Eur Soc Ther Radiol Oncol 2007;82:254–64. https://doi.org/10.1016/j.radonc.2006.12.008.

16. Haussmann J, Corradini S, Nestle-Kraemling C, Bölke E, Njanang FJD, Tamaskovics B, et al. Recent advances in radiotherapy of breast cancer. Radiat Oncol Lond Engl 2020;15. https://doi.org/10.1186/s13014-020-01501-x.

17. Alexander A, Soisson E, Hijal T, Sarfehnia A, Seuntjens J. Comparison of modulated electron radiotherapy to conventional electron boost irradiation and volumetric modulated photon arc therapy for treatment of tumour bed boost in breast cancer. Radiother Oncol J Eur Soc Ther Radiol Oncol 2011;100:253–8. https://doi.org/10.1016/j.radonc.2011.05.081.

18. an Parijs H, Reynders T, Heuninckx K, Verellen D, Storme G, De Ridder M. Breast conserving treatment for breast cancer: dosimetric comparison of different non-invasive techniques for additional boost delivery. Radiat Oncol Lond Engl 2014;9:36. https://doi.org/10.1186/1748-717X-9-36.

19. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–4. https://doi.org/10.1245/s10434-010-0985-4.

20. Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Biete Sola A, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. Radiother Oncol J Eur Soc Ther Radiol Oncol 2015;114:3–10. https://doi.org/10.1016/j.radonc.2014.11.030.

21. ICRU Report 50, Prescribing, Recording, and Reporting Photon Beam Therapy – ICRU n.d. https://www.icru.org/report/prescribing-recording-and-reporting-photon-beam-therapy-report-50/ (accessed June 10, 2022).

22. ICRU Report 62, Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU 50) – ICRU n.d. https://www.icru.org/report/prescribing-recording-and-reporting-photon-beam-therapy-report-62/ (accessed June 10, 2022).

23. CRU Report 83, Prescribing, Recording, and Reporting Intensity-Modulated Photon-Beam Therapy (IMRT) – ICRU n.d. https://www.icru.org/report/prescribing-recording-and-reporting-intensity-modulated-photon-beam-therapy-imrticru-report-83/ (accessed June 10, 2022).

24. Feuvret L, Noël G, Mazeron J-J, Bey P. Conformity index: a review. Int J Radiat Oncol Biol Phys 2006;64:333–42. https://doi.org/10.1016/j.ijrobp.2005.09.028.

25. Nielsen MH, Berg M, Pedersen AN, Andersen K, Glavicic V, Jakobsen EH, et al. Delineation of target volumes and organs at risk in adjuvant radiotherapy of early breast cancer: national guidelines and contouring atlas by the Danish Breast Cancer Cooperative Group. Acta Oncol Stockh Swed 2013;52:703–10. https://doi.org/10.3109/0284186X.2013.765064.

26. Killander F, Wieslander E, Karlsson P, Holmberg E, Lundstedt D, Holmberg L, et al. No Increased Cardiac Mortality or Morbidity of Radiation Therapy in Breast Cancer Patients After Breast-Conserving Surgery: 20-Year Follow-up of the Randomized SweBCGRT Trial. Int J Radiat Oncol Biol Phys 2020;107:701–9. https://doi.org/10.1016/j.ijrobp.2020.04.003.

27. Stovall M, Smith SA, Langholz BM, Boice JD, Shore RE, Andersson M, et al. Dose to the contralateral breast from radiotherapy and risk of second primary breast cancer in the WECARE study. Int J Radiat Oncol Biol Phys 2008;72:1021–30. https://doi.org/10.1016/j.ijrobp.2008.02.040.

28. Fiorentino A, Gregucci F, Mazzola R, Figlia V, Ricchetti F, Sicignano G, et al. Intensity-modulated radiotherapy and hypofractionated volumetric modulated arc therapy for elderly patients with breast cancer: comparison of acute and late toxicities. Radiol Med (Torino) 2019;124:309–14. https://doi.org/10.1007/s11547-018-0976-2.

29. sang Y, Ciurlionis L, Kirby AM, Locke I, Venables K, Yarnold JR, et al. Clinical impact of IMPORT HIGH trial (CRUK/06/003) on breast radiotherapy practices in the United Kingdom. Br J Radiol 2015;88. https://doi.org/10.1259/bjr.20150453.

30. Meng J, Huang W, Mei X, Yu X, Pan Z, Ma J, et al. Adjuvant breast inversely planned intensity-modulated radiotherapy with simultaneous integrated boost for early stage breast cancer : Results from a phase II trial. Strahlenther Onkol Organ Dtsch Rontgengesellschaft Al 2020. https://doi.org/10.1007/s00066-020-01611-1.

31. Cozzi L, Lohr F, Fogliata A, Franceschini D, De Rose F, Filippi AR, et al. Critical appraisal of the role of volumetric modulated arc therapy in the radiation therapy management of breast cancer. Radiat Oncol Lond Engl 2017;12. https://doi.org/10.1186/s13014-017-0935-4.

32. Lee H-H, Hou M-F, Chuang H-Y, Huang M-Y, Tsuei L-P, Chen F-M, et al. Intensity modulated radiotherapy with simultaneous integrated boost vs. conventional radiotherapy with sequential boost for breast cancer - A preliminary result. Breast Edinb Scotl 2015;24:656–60. https://doi.org/10.1016/j.breast.2015.08.002.

33. Hörner-Rieber J, Forster T, Hommertgen A, Haefner MF, Arians N, König L, et al. Intensity-modulated radiotherapy (IMRT) with simultaneously integrated boost shortens treatment time and is non-inferior to conventional radiotherapy followed by sequential boost in adjuvant breast cancer treatment: results of a large randomized phase III trial (IMRT-MC2 trial). Int J Radiat Oncol Biol Phys 2020. https://doi.org/10.1016/j.ijrobp.2020.12.005.

34. Small K, Kelly C, Beldham-Collins R, Gebski V. Whole breast and excision cavity radiotherapy plan comparison: Conformal radiotherapy with sequential boost versus intensity-modulated radiation therapy with a simultaneously integrated boost. J Med Radiat Sci 2013;60:16–24. https://doi.org/10.1002/jmrs.4.

35. Rudat V, Nour A, Alaradi AA, Mohamed A, Altuwaijri S. In vivo surface dose measurement using GafChromic film dosimetry in breast cancer radiotherapy: comparison of 7-field IMRT, tangential IMRT and tangential 3D-CRT. Radiat Oncol Lond Engl 2014;9:156. https://doi.org/10.1186/1748-717X-9-156.

36. Nissen HD, Appelt AL. Improved heart, lung and target dose with deep inspiration breath hold in a large clinical series of breast cancer patients. Radiother Oncol 2013;106:28–32. https://doi.org/10.1016/j.radonc.2012.10.016.

37. Michalski A, Atyeo J, Cox J, Rinks M, Morgia M, Lamoury G. A dosimetric comparison of 3D-CRT, IMRT, and static tomotherapy with an SIB for large and small breast volumes. Med Dosim 2014;39:163–8. https://doi.org/10.1016/j.meddos.2013.12.003.

38. Meyer P, Niederst C, Scius M, Jarnet D, Dehaynin N, Gantier M, et al. Is the lack of respiratory gating prejudicial for left breast TomoDirect treatments? Phys Med 2016;32:644–50. https://doi.org/10.1016/j.ejmp.2016.04.001.

39. Joseph B, Farooq N, Kumar S, Vijay CR, Puthur KJ, Ramesh C, et al. Breast-conserving radiotherapy with simultaneous integrated boost; field-in-field three-dimensional conformal radiotherapy versus inverse intensity-modulated radiotherapy - A dosimetric comparison: Do we need intensity-modulated radiotherapy? South Asian J Cancer 2018;7:163–6. https://doi.org/10.4103/sajc.sajc_82_18.

40. van der Laan HP, Dolsma WV, Schilstra C, Korevaar EW, de Bock GH, Maduro JH, et al. Limited benefit of inversely optimised intensity modulation in breast conserving radiotherapy with simultaneously integrated boost. Radiother Oncol J Eur Soc Ther Radiol Oncol 2010;94:307–12. https://doi.org/10.1016/j.radonc.2010.01.024.

41. Balaji K, Balaji Subramanian S, Sathiya K, Thirunavukarasu M, Anu Radha C, Ramasubramanian V. Hybrid planning techniques for hypofractionated whole-breast irradiation using flattening filter-free beams. Strahlenther Onkol 2020;196:376–85. https://doi.org/10.1007/s00066-019-01555-1.

42. Lin J-F, Yeh D-C, Yeh H-L, Chang C-F, Lin J-C. Dosimetric comparison of hybrid volumetric-modulated arc therapy, volumetric-modulated arc therapy, and intensity-modulated radiation therapy for left-sided early breast cancer. Med Dosim Off J Am Assoc Med Dosim 2015;40:262–7. https://doi.org/10.1016/j.meddos.2015.05.003.

43. ONAL C, EFE E, GULER OC, YILDIRIM BA. Dosimetric Comparison of Sequential Versus Simultaneous-integrated Boost in Early-stage Breast Cancer Patients Treated With Breast-conserving Surgery. In Vivo 2019;33:2181–9. https://doi.org/10.21873/invivo.11720.

44. Aly MMOM, Abo-Madyan Y, Jahnke L, Wenz F, Glatting G. Comparison of breast sequential and simultaneous integrated boost using the biologically effective dose volume histogram (BEDVH). Radiat Oncol Lond Engl 2016;11:16. https://doi.org/10.1186/s13014-016-0590-1.

45. Van Parijs H, Reynders T, Heuninckx K, Verellen D, Storme G, De Ridder M. Breast conserving treatment for breast cancer: dosimetric comparison of sequential versus simultaneous integrated photon boost. BioMed Res Int 2014;2014:827475. https://doi.org/10.1155/2014/827475.

46. Xi D, Ding Y, Hu R, Gu W, Mu J-M, Li Q-L. Advantages of a technique using two 50 degree arcs in simultaneous integrated boost radiotherapy for left-sidebreast cancer. Sci Rep 2017. https://doi.org/10.1038/s41598-017-15307-7.

47. Piras A, Menna S, D'Aviero A, Marazzi F, Mazzini A, Cusumano D, Massaccesi M, Mattiucci GC, Daidone A, Valentini V, Boldrini L. New fractionations in breast cancer: a dosimetric study of 3D-CRT versus VMAT. https://doi.org/10.1002/jmrs.530

JMRO

Journal of Medical and Radiation Oncology

Journal homepage: www.jmedradonc.org

Pineoblastomas in Pediatric Patients: A Single Institutional Experience

Răzvan Lăpădat[1]

[1] *Department of Pathology, Pathology Specialists of Memphis, Methodist Le Bonheur Healthcare, Memphis, Tennessee*

Corresponding author: Răzvan Lăpădat; **e-mail**: rlapadat@gmail.com

Abstract

Pineoblastomas are rare, malignant pineal parenchymal tumors encountered predominantly in pediatric patients. They are distinct from primitive neuroectodermal tumors (PNET) at other sites in that they exhibit photosensory differentiation including Flexner–Wintersteiner rosettes and fleurettes. Diagnosis can be challenging since they share morphologic and immunohistochemical features with other embryonal tumors and the developing pineal gland. Pineal anlage tumor is a rare variant of pineoblastoma defined by divergent neuroepithelial and ectomesenchymal differentiation without an endodermal component. To date the five published cases of anlage tumors behaved aggressively. We describe a case series which includes one patient with pineal anlage tumor and the clinical, radiological and pathological characteristics of pediatric pineoblastomas.

Keywords: *pineoblastoma, immunohistochemistry, pediatric tumors, anlage tumors, primitive neuroectodermal tumors/PNET*

Origininal Research

1. Introduction

Pineoblastomas (PBs) are rare, highly malignant (grade IV in the 2021 World Health Organization (WHO) classification of the tumors of the central nervous system (CNS) (1) pineal parenchymal tumors (PPT) occurring mainly in the pediatric population. They are part of the broad category of central primitive neuro-ectodermal tumors (cPNET) and may exhibit photosensory differentiation including Flexner–Wintersteiner rosettes and fleurettes (2). Diagnosis can be challenging since they share morphologic and immunohistochemical features with other embryonal tumors and the developing pineal gland (2). Pineal anlage tumor is a rare variant of PB. It is defined by divergent neuroepithelial and ectomesenchymal differentiation without an endodermal component

https://doi.org/10.53011/JMRO.2022.01.05

Published by Casa Cărții de Știință

(2). The few published cases of anlage tumors behaved aggressively (3-5).

We describe the clinicopathologic characteristics of thirteen pediatric cases of PBs and compare responses to therapy and prognosis to better understand the clinical course of PBs in the pediatric population.

2. Material and Methods

Pathology records from 1980 to 2012 were searched for PBs at a tertiary pediatric hospital (Children Hospital Wisconsin). Thirteen consecutive cases of PBs, consisting of 12 classical PBs and one anlage tumor were identified. Cases were reviewed and classified using the presence/absence of anlage/divergent differentiation component, rosette formation, pigment production, mitoses and necrosis. Radiology reports and clinical data were reviewed. Formalin fixed, paraffin-embedded tissue was sectioned and stained with hematoxylin and eosin. We assessed the histologic diagnoses according to the 2021 WHO classification of tumors of the CNS (1). Mitoses were counted in 10 high-power fields (HPF, 400x) and expressed as the number of mitoses per 10 consecutive HPFs. Immunohistochemistry was performed with the following commercially available antibodies: anti-synaptophysin (SY38, mouse, monoclonal, 1:100, catalog# IS776, Dako, Tokyo, Japan), glial fibrillary acidic protein (GFAP) (polyclonal, rabbit, 1:4000, catalog# Z0334, Dako,Glostrup, Denmark), vimentin (clone V9, mouse, monoclonal, 1:1000, catalog# M0725, Dako, Tokyo, Japan), anti-neurofilament (2F11, mouse, monoclonal, 1:50, catalog# M0762, Dako, Tokyo, Japan), antineuronal nuclear antigen (anti-NeuN; A60, 1:100, catalog# MAB377 Millipore, Billerica, Massachusetts, USA), and anti-Ki67 (MIB-1, mouse, monoclonal, 1:100, catalog# IS626, Dako, Tokyo, Japan). The MIB-1 indices represent rate of immunopositive cells, determined by examining more than 1000 tumor cells.

3. Results

Histopathology

Microscopic examination showed densely cellular neoplasms composed of sheets of haphazardly arranged, variably sized immature cells with scant eosinophilic cytoplasm. The smaller cells had small angulated to oval nuclei with hyperchromatic smudged nuclear chromatin and indistinct nucleoli. The larger cells had lobulated vesicular nuclei with small nucleoli and moderately abundant granular to eccentric glassy eosinophilic cytoplasm. Mitotic figures were present from rare mitoses (1-2/10HPF) to 40/10 HPF in one instance. Variable degrees of apoptosis, necrosis and karyorrhexis were noted. In areas the sheets of tumor cells were interrupted by interspersed bands of fibrovascular stroma with scattered blood vessels. Rosette-like formations were variably present. The average MIB-1 index was 41% (median is best) (range 30-60%). The anlage tumor had areas of glioneuronal differentiation (Figure 1C) alternating with areas of high grade small round blue cells with focal/minimal necrosis (Figure 1B), morphologically similar to medulloblastoma. Homer Wright and Flexner-Wintersteiner rosettes were present. Melanin production, cartilaginous, and rhabdomyoblastic differentiation were also present (Figure 1A). Immunoperoxidase stains for synaptophysin was diffusely positive (Figure 1E). while glial fibrillary acidic protein (Figure 1D) is negative. The MIB1 index was 50% (Figure 1F).

Clinical characteristics

We report thirteen cases of biopsy-proven PBs including one anlage tumor (Table 1). The female to male ratio was 2.2 and the age ranged from 8 months to 17 years (median 10 years). The radiological findings by brain computer tomography (CT) scan and magnetic resonance imaging (MRI) showed heterogeneous enhancing, lobulated pineal gland lesions with dimensions ranging from 2.5 to 5 cm. Hydrocephalus was identified in nine (69%) patients. Five cases (38.4%) had spinal cord metastasis, three (23%) were negative for what (cerebrospinal fluid) CSF dissemination and no information was available in the remaining five cases (38.4%). Nine patients (69%) received a combination of surgical resection, irradiation (whole brain: 7, craniospinal: 3) and chemotherapy and one patient had a combination of resection and irradiation.

Table 1

Case no.	Age at diagnosis	Gender	Therapy	Hydrocephalus	Outcome	Survival from initial Dx
1	12 y	M	resection and XRT	Yes	Alive	**19 y**
2	11 y	F	NA	N/A	Alive	**22 y**
3	11 y	M	resection, XRT and chemo	Yes	Alive	**6 y**
4	10 y	M	resection, XRT and chemo	N/A	Alive	**16 y**
5*	11 mo	F	resection, XRT and chemo	Yes	Alive	**12 mo**
6	17 y	F	resection, XRT and chemo	Yes	Alive	**12 y**
7	8 mo	F	NA	N/A	Deceased	**(3 yo)**
8	4 y	M	resection, XRT and chemo	Yes	Deceased	**(11 yo)**
9	9 y	F	resection, XRT and chemo	Yes	Deceased	**(13 yo)**
10	5 y	F	resection, XRT and chemo	No	Alive	**6 mo**
11	13 y	F	resection, XRT and chemo	Yes	Deceased	**(18 yo)**
12	4 y	F	NA	Yes	Alive	**15 y**
13	**11 y**	**F**	**resection, XRT and chemo**	**Yes**	**Alive**	**25 y**

Legend:*- Anlage tumor;
XRT- Radiation therapy; Dx- diagnosis

Two of these patients (15.4%) had third ventriculostomy due to severe headache and altered consciousness (secondary to hydrocephalus). No information was available regarding treatment of three (23%) patients. Nine patients (69%) are alive with survival times between 6 months and 25 years (median 13 years). Four patients (30.7%) died, with an average survival time from the diagnosis of 4.25 years (range 2-6 years). The mean duration of follow-up was 14.5 months (range: 6 months-25 years). The anlage tumor was diagnosed in a 11- month-old female. The MRI of the brain showed a focally enhancing, well circumscribed, lobulated pineal gland mass lesion (44.6 mm x 45.6 mm x 43.3 mm) with attenuated apparent diffusion coefficient (ADC) signal on diffusion-weighted imaging MRI and prominent calcification along its posterior right margin on CT (Figure 1). MRI of the cervical spine appeared unremarkable without evidence of tumor seeding. Adjuvant therapy was given using high dose methotrexate arm of ACNS0334 Phase III clinical trial with induction therapy to include 3 cycles of vincristine, high-dose methotrexate, etoposide, cyclophosphamide, and cisplatin and consolidation therapy to include 3 cycles of carboplatin and thiotepa with autologous stem cell rescue. This regimen has been chosen based upon its potential effectiveness towards the embryonal (PB) component of the tumor. The patient is free of disease 12 months after the diagnosis.

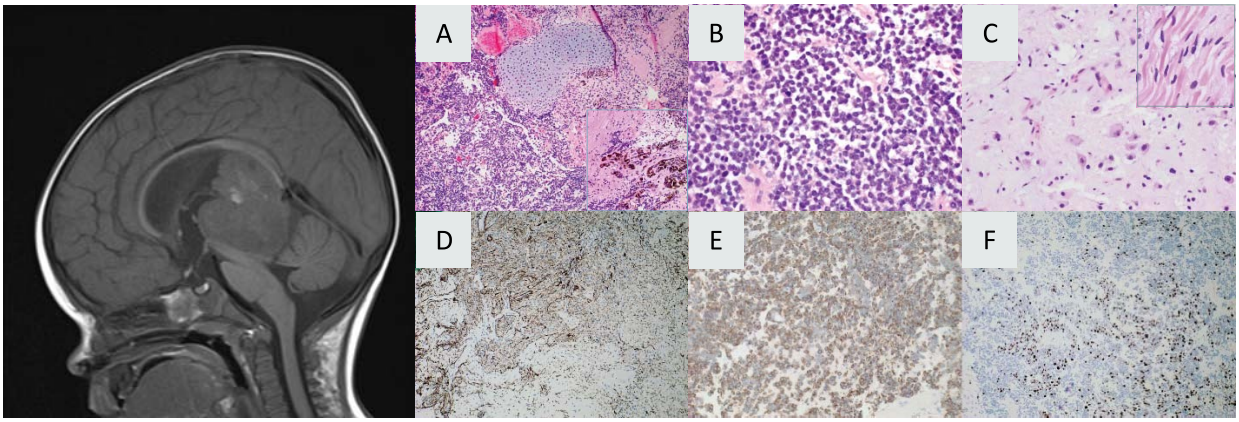


Figure 1: 11-month-old female with pineal anlage tumor: Sagittal, T1-weigthed sequence without contrast shows a large, well-circumscribed, lobulated hypointense pineal region mass (left). Histologic sections show melanin production and cartilaginous differentiation (A, 100x), alternating with areas of high grade small round blue cells with focal/minimal necrosis, Homer Wright and Flexner-Wintersteiner rosettes (B, 200x) admixed with rhabdomyoblastic and glioneuronal differentiation (C, 400 x). GFAP is negative (D, 200x), synaptophysin demonstrates diffuse positivity (E, 200x) while mitoses are common and the MIB1 index is approximated at 50% (F, 200x).

4. Discussion

Pineal parenchymal tumors (PPTs) are a subcategory of primary neoplasms of the pineal gland. They comprise less than 1% of all brain tumors and are most commonly diagnosed in pediatric patients or young adults. They include PBs, pineocytomas, and pineal parenchymal tumors of intermediate differentiation (PPTID). The 2021 WHO Classification of Tumors of the Central Nervous System added desmoplastic myxoid tumour of the pineal region and SMARCB1-mutant tumor. In light of the 2021 WHO classification, molecular subtyping of pineoblastomas is becoming increasingly important (1, 17, 45). Pineocytomas are well-differentiated, less aggressive tumors composed of cells with abundant eosinophilic cytoplasm and pineocytic rosette formation (1, 6). PPTID have features intermediate between those of well-differentiated PCs and undifferentiated PBs show a cellular milieu that is less dense but with limited differentiation or rosette formation (1). PBs are primitive small round blue cell tumors that resemble medulloblastomas, with a strong potential for leptomeningeal seeding (7,8). In several published case series PBs were the most common type of PPTs, representing up to half of all PPTs (5,9,10). Extracranial metastasis to the peritoneal cavity can occur via ventriculoperitoneal shunts. Rare metastases to the bone (11) and lung (8) have been described. Similar to central nervous system primitive neuroectodermal tumors, the prognosis for patients with PBs is very poor, with 5-year survival rates of only 10% (5,10,12). Compared to other primary pineal tumors, anlage tumors have neuroepithelial and ectomesenchymal differentiation but lack endodermal differentiation. They are extremely rare and have been only recently mentioned as a provisional entity in the WHO classification system, but are not recognized as a separate entity (1,13). Schmidbauer et al. (4) first described this tumor in 1989, reporting a 9-year-old female with a primitive pineal tumor. Only a few cases have since been reported and showed that pineal anlage tumors include immature cartilage, skeletal muscle, and melanin pigmented cells as well as Homer Wright and Flexner-Wintersteiner rosettes (31). Most reported patients presented with hydrocephalus, but some had spasticity and ataxic gait (9,14,15). Patients with pineal anlage tumors have previously been given a prognosis similar to classical PBs (3,16). Including our case, only 6 cases have been reported thus far to the best of our knowledge, so the significance, prognosis, and treatment of pineal anlage tumors are uncertain.

On brain CT imaging PBs appear as large, lobulated mass lesions and usually show

heterogeneous contrast enhancement (6,14). Hydrocephalus is often present and the tumors show variable degrees of cystic changes. On MRI, PBs are hypo- to isointense on T1-weighted images and hyperintense on T2-weighted images with heterogeneous contrast enhancement (6,14,15,17). The interface between the tumor and surrounding structures is sometimes poorly defined (6,14).

On gross pathological examination PBs are pink-tan soft, gelatinous tumors, occasionally showing diffuse infiltration of surrounding tissues (7). Hemorrhage and necrosis are often encountered (7–9,18–20). Microscopically they appear as patternless sheets of small cells with scant cytoplasm, hyperchromatic nuclei, high nucleocytoplasmic ratios, and scant cytoplasm (3,21). Lobular architecture is absent (6). Necrosis is common but mitotic activity is variable. Frequent Homer-Wright rosettes (Figure 1) and occasional Flexner-Wintersteiner rosettes are identified.

Pineocytomatous rosettes are absent. Rare bundles of cytoplasmic processes (fleurettes) showing bulbous expansion at their distal portion can be seen and indicate photoreceptor differentiation (21,22). Silver staining highlights the scant cytoplasm and few cellular processes. Melanin production as well as cartilaginous and rhabdomyoblastic differentiation are encountered in pineal anlage tumors (4,23).

PBs show expression of neuronal and photoreceptor markers. Immunolabeling of neuron-specific enolase and synaptophysin is weak and diffuse compared to other pineal parenchymal tumors. Labeling for neurofilaments, class III *β*-tubulin, chromogranin A, and retinal S-antigen is focal (19,24–28). Rare cases show focal positivity for glial fibrillary acidic protein *α*B-crystallin, warranting careful exclusion of entrapped reactive astrocytes (2,13). Flexner-Wintersteiner rosettes and fleurettes are strongly positive for retinal S-antigen. Hence, PBs have common morphological and immunohistochemical features with photoreceptor cells of the developing pineal gland and retina. The average MIB-1 labeling index is significantly higher in PBs than in other PPTs, with average values of 24% to 27% (29–31).

The ultrastructure of PBs is similar to other poorly differentiated neuroectodermal tumors and shows no recognizable neuronal structures. Tumors are composed of sheets of small cells with round to oval nuclei which are often irregularly indented, with scant cytoplasm, containing few organelles as annulate lamellae, endoplasmic reticulum (smooth and rough), membranous whorls and occasional microtubules, intermediate filaments and lysozomes (25,32–35). Junctional complexes are usually inconspicuous. Compared to pineocytomas, PBs have rare dense core vesicles (33,34). Poorly formed, short cell processes containing microtubules and a few dense core vesicles can be seen (6,34). In some instances of photoreceptor differentiation, such as synaptic ribbons, microtubular sheaves, and club-shaped giant cilia with a 9 + 0 configuration is observed (32–35).

Molecular and genetic alterations underlying the formation of PPTs have not been well defined. Cytogenetic studies have suggested that distal monosomy 12q and partial deletion or loss of chromosome 11 are related to tumor progression (36–38). Monosomy of chromosomes 20 and 22, and trisomy of chromosome 14 have also been described (24). Two studies reported INI1 gene (22q11) mutations (39,40). Patients with RB1 gene abnormalities PBs have a significantly worse prognosis compared to sporadic cases (41). PBs develop in patients with familial bilateral retinoblastomas, an occurrence termed ‘trilateral retinoblastoma syndrome (17,42), and have also been reported in patients with familial adenomatous polyposis (43). One study using RT-PCR analysis identified a higher expression of four genes (*PRAME, CD24, POU4F2,* and *HOXD13*) in PBs and PPTID, in contrast to pineocytomas (37). Patients with signs of elevated intracranial pressure (ICP) (papilledema, decreased visual acuity) and obstructive hydrocephalus should be admitted for urgent CSF diversion.

Given the propensity of certain pineal tumors to metastasize to the spinal column (PB, ependymoma, or germinoma), a baseline contrast enhanced MRI of the entire spinal axis should be obtained. In addition to further imaging, the presence of a pineal tumor should

also prompt sampling of Germ-Cell Tumors (GCT) markers (□-human chorionic gonadotropin or □-fetoprotein) from serum and/or CSF. Since most patients with pineal tumors present with symptoms related to hydrocephalus, a shunt. Either procedure allows for both CSF sampling and alleviation of obstructive hydrocephalus, which is the most pressing concern during acute management of patients with PB. Patients with CSF positive for GCT markers should then receive adjuvant therapy without the need for further surgical intervention. The treatment of choice for most PPTs, including PBs, remains open surgical resection. Open surgery allows for adequate tissue sampling and improved diagnostic accuracy, which is critical for effective management of pineal lesions. In addition, aggressive surgical resection is associated with improved outcome in both pineocytoma (gross total resection is often curative, obviating the need for adjuvant therapy) and PB (gross total resection results in prolonged survival). Standard adjuvant therapy for pathology-confirmed PB after maximal surgical resection includes fractionated radiotherapy and chemotherapy. Typical radiotherapy protocols for PB are 5500 cGy to the tumor region and 3500 cGy to the spinal axis (2 Gy fractions). Chemotherapy protocols are less consistent among centers but usually include 2 to 3 agents selected from vincristine, cisplatin/carboplatin, cyclophosphamide, etoposide, and CCNU (lomustine). In addition to these standard therapies, more recent modalities such as Gamma Knife radiotherapy have been suggested as an adjunct to conventional radiotherapy or as a substitute for surgical resection, but definitive data are lacking. Several promising experimental therapies are being evaluated for the treatment of PB, including vorinostat (a histone deacetylase inhibitor), retinoic acid, and high-dose chemotherapy with autologous stem cell rescue (44).

5. Conclusions

PBs are uncommon pediatric tumors. Diagnosis can be difficult as the surgical biopsy material is often limited in quality and quantity and the tumor lacks a distinctive immunophenotype. In our study the majority of patients (69%) did well with appropriate therapy. Adequate follow up in order to detect the possibility of recurrence or dissemination is warranted. Further studies are needed to better classify pineal tumors and, in light of the latest 2021 WHO classification molecular subtyping of these unusual pediatric brain tumors is highly recommended.

Abbreviations:

2F11 - anti-neurofilament antibody
ADC - apparent diffusion coefficient
Anti-NeuN - antineuronal nuclear antigen antibody
CCNU - lomustine
CD4 - cluster of differentiation 4
CNS - Central Nervous System
CSF - cerebrospinal fluid
cPNET - central primitive neuroectodermal tumors
GCT- Germ - Cell Tumors
GFAP- glial fibrillary acidic protein
HOXD13 - homebox B13
ICP - intracranial pressure
PBs - pineoblastomas
PNETs - primitive neuroectodermal tumors
POU4F2 - POU Class 4 Homeobox 2
PPTs - pineal parenchymal tumours
PPTID - pineal parenchymal tumors of intermediate differentiation
PRAME - preferentially expressed antigen in melanoma

MIB-1 - mindbomb antibody
MRI - magnetic resonance imaging
SMARCB1 - SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1
SY 38 - anti-synaptophysin antibodies
WHO - World Health Organisation

Statements:

Authors' contribution: RL worked on the design, interpretation of the results and wrote the manuscript.

Consent for publication: As the corresponding author, I read and approved the manuscript.

Conflict of interests: The author declares no conflict of interest.

Funding Sources: None

Statement of Ethics: Non applicable

Acknowledgments: The author would like to thank Drs. Annette Segura and Gabriela Gheorghe, Department of Pathology and Laboratory Medicine, Children's Hospital of Wisconsin, Milwaukee, WI for providing feedback to the manuscript.

References:

1. WHO Classification of Tumours Editorial Board. World Health Organization Classification of Tumours of the Central Nervous System. 5th ed. Lyon: International Agency for Research on Cancer; 2021

2. Louis, D. N., Deutsches Krebsforschungszentrum Heidelberg, International Agency for Research on Cancer & World Health Organization. WHO classification of tumours of the central nervous system. (Distributed by WHO Press, World Health Organization, 2007). At <http://site.ebrary.com/id/10214529>

3. Ahuja, A. et al. Pineal anlage tumour - a rare entity with divergent histology. J. Clin.Neurosci. Off. J. Neurosurg. Soc. Australas. 18, 811–813 (2011).

4. Schmidbauer, M., Budka, H. & Pilz, P. Neuroepithelial and ectomesenchymal differentiation in a primitive pineal tumor ('pineal anlage tumor'). Clin. Neuropathol. 8, 7–10 (1989).

5. Fauchon, F. et al. Parenchymal pineal tumors: a clinicopathological study of 76 cases. Int. J.Radiat. Oncol. Biol. Phys. 46, 959–968 (2000).

6. Sato, K. & Kubota, T. Pathology of pineal parenchymal tumors. Prog. Neurol. Surg. 23, 12–25 (2009).

7. Borit, A., Blackwood, W. & Mair, W. G. The separation of pineocytoma from

pineoblastoma. Cancer 45, 1408–1418 (1980).

8. Banerjee, A. K. & Kak, V. K. Pineoblastoma with spontaneous intra and extracranial metastasis. J. Pathol. 114, 9–12 (1974).

9. Schild, S. E. et al. Pineal parenchymal tumors. Clinical, pathologic, and therapeutic aspects. Cancer 72, 870–880 (1993).

10. Han, S. J., Clark, A. J., Ivan, M. E., Parsa, A. T. & Perry, A. Pathology of pineal parenchymal tumors. Neurosurg. Clin. N. Am. 22, 335–340, vii (2011).

11. Constantine, C., Miller, D. C., Gardner, S., Balmaceda, C. & Finlay, J. Osseous metastasis of pineoblastoma: a case report and review of the literature. J. Neurooncol. 74, 53–57 (2005).

12. Al-Hussaini, M., Sultan, I., Abuirmileh, N., Jaradat, I. & Qaddoumi, I. Pineal gland tumors: experience from the SEER database. J. Neurooncol. 94, 351–358 (2009).

13. Dahiya, S. & Perry, A. Pineal tumors. Adv. Anat. Pathol. 17, 419–427 (2010).

14. Chiechi, M. V., Smirniotopoulos, J. G. & Mena, H. Pineal parenchymal tumors: CT and MR features. J. Comput. Assist. Tomogr. 19, 509–517 (1995).

15. Nakamura, M. et al. Neuroradiological characteristics of pineocytoma and pineoblastoma.Neuroradiology 42, 509–514 (2000).

16. Olaya, J. E., Raghavan, R., Totaro, L. & Zouros, A. Pineal anlage tumor in a 5-month-old boy. J. Neurosurg. Pediatr. 5, 636–640 (2010).

17. Provenzale, J. M., Weber, A. L., Klintworth, G. K. & McLendon, R. E. Radiologic-pathologic correlation. Bilateral retinoblastoma with coexistent pinealoblastoma (trilateral retinoblastoma). AJNR Am. J. Neuroradiol. 16, 157–165 (1995).

18. Herrick, M. K. & Rubinstein, L. J. The cytological differentiating potential of pineal parenchymal neoplasms (true pinealomas). A clinicopathological study of 28 tumours. Brain J. Neurol. 102, 289–320 (1979).

19. Mena, H., Rushing, E. J., Ribas, J. L., Delahunt, B. & McCarthy, W. F. Tumors of pineal parenchymal cells: a correlation of histological features, including nucleolar organizer regions, with survival in 35 cases. Hum. Pathol. 26, 20–30 (1995).

20. DeGirolami, U. & Schmidek, H. Clinicopathological study of 53 tumors of the pineal region. J. Neurosurg. 39, 455–462 (1973).

21. Herrick, M. K. & Rubinstein, L. J. The cytological differentiating potential of pineal parenchymal neoplasms (true pinealomas). A clinicopathological study of 28 tumours. Brain J. Neurol. 102, 289–320 (1979).

22. Stefanko, S. Z. & Manschot, W. A. Pinealoblastoma with retinoblastomatous differentiation. Brain J. Neurol. 102, 321–332 (1979).

23. Berns, S. & Pearl, G. Review of pineal anlage tumor with divergent histology. Arch. Pathol.Lab. Med. 130, 1233–1235 (2006).

24. Russell and Rubinstein's pathology of tumors of the nervous system. (Hodder Arnold; Distributed in the United States of America by Oxford University Press, 2006).

25. Numoto, R. T. Pineal parenchymal tumors: cell differentiation and prognosis. J. Cancer Res. Clin. Oncol. 120, 683–690 (1994).

26. Perentes, E., Rubinstein, L. J., Herman, M. M. & Donoso, L. A. S-antigen immunoreactivity in human pineal glands and pineal parenchymal tumors. A monoclonal antibody study. Acta Neuropathol. (Berl.) 71, 224–227 (1986).

27. Yamane, Y., Mena, H. & Nakazato, Y. Immunohistochemical characterization of pineal parenchymal tumors using novel monoclonal antibodies to the pineal body. Neuropathol. Off. J. Jpn. Soc. Neuropathol. 22, 66–76 (2002).

28. Jouvet, A. et al. Pineal parenchymal tumors: a correlation of histological features with prognosis in 66 cases. Brain Pathol. Zurich Switz. 10, 49–60 (2000).

29. Arivazhagan, A., Anandh, B., Santosh, V. & Chandramouli, B. A. Pineal parenchymal tumors--utility of immunohistochemical markers in prognostication. Clin. Neuropathol. 27, 325–333 (2008).

30. Rickert, C. H., Simon, R., Bergmann, M., Dockhorn-Dworniczak, B. & Paulus, W. Comparative genomic hybridization in pineal parenchymal tumors. Genes. Chromosomes Cancer 30, 99–104 (2001).

31. Tsumanuma, I., Tanaka, R. & Washiyama, K. Clinicopathological study of pineal parenchymal tumors: correlation between histopathological features, proliferative potential, and prognosis. Brain Tumor Pathol. 16, 61–68 (1999).

32. Jouvet, A. et al. Structural and ultrastructural characteristics of human pineal gland, and pineal parenchymal tumors. Acta Neuropathol. (Berl.) 88, 334–348 (1994).

33. Min, K. W., Scheithauer, B. W. & Bauserman, S. C. Pineal parenchymal tumors: an ultrastructural study with prognostic implications. Ultrastruct. Pathol. 18, 69–85 (1994).

34. Markesbery, W. R., Haugh, R. M. & Young, A. B. Ultrastructure of pineal parenchymal neoplasms. Acta Neuropathol. (Berl.) 55, 143–149 (1981).

35. Kline, K. T., Damjanov, I., Katz, S. M. & Schmidek, H. Pineoblastoma: an electron microscopic study. Cancer 44, 1692–1699 (1979).

36. Bello, M. J., Rey, J. A., de Campos, J. M. & Kusak, M. E. Chromosomal abnormalities in a pineocytoma. Cancer Genet. Cytogenet. 71, 185–186 (1993).

37. Rainho, C. A., Rogatto, S. R., de Moraes, L. C. & Barbieri-Neto, J. Cytogenetic study of a pineocytoma. Cancer Genet. Cytogenet. 64, 127–132 (1992).

38. Sreekantaiah, C., Jockin, H., Brecher, M. L. & Sandberg, A. A. Interstitial deletion of chromosome 11q in a pineoblastoma. Cancer Genet. Cytogenet. 39, 125–131 (1989).

39. Biegel, J. A. et al. Mutations of the INI1 rhabdoid tumor suppressor gene in medulloblastomas and primitive neuroectodermal tumors of the central nervous system. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 6, 2759–2763 (2000).

40. Miller, S., Ward, J. H., Rogers, H. A., Lowe, J. & Grundy, R. G. Loss of INI1 protein expression defines a subgroup of aggressive central nervous system primitive neuroectodermal tumors. Brain Pathol. Zurich Switz. 23, 19–27 (2013).

41. Plowman, P. N., Pizer, B. & Kingston, J. E. Pineal parenchymal tumours: II. On the aggressive behaviour of pineoblastoma in patients with an inherited mutation of the RB1 gene. Clin. Oncol. R. Coll. Radiol. G. B. 16, 244–247 (2004).

42. Bader, J. L. et al. Trilateral retinoblastoma. Lancet Lond. Engl. 2, 582–583 (1980).

43. Gadish, T., Tulchinsky, H., Deutsch, A. A. & Rabau, M. Pinealoblastoma in a patient with familial adenomatous polyposis: variant of Turcot syndrome type 2? Report of a case and review of the literature. Dis. Colon Rectum 48, 2343–2346 (2005).

44. Tate, M. C., Rutkowski, M. J. & Parsa, A. T. Contemporary management of pineoblastoma. Neurosurg. Clin. N. Am. 22, 409–412, ix (2011).

45. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021 Aug 2;23(8):1231-1251.

JMRO

Journal of Medical and Radiation Oncology

Journal homepage: www.jmedradonc.org

Real-World Treatment Patterns and Recurrence Rates in Cutaneous Melanoma Patients – A Single Romanian Center Experience

Dan Corneliu Jinga[1], Ioana Lazăr[1], Maria-Ruxandra Jinga[2], Andrea Crăciunescu[1] and Alexandru Blidaru[3,4]

[1] *Department of Oncology, Neolife Bucharest Medical Center, Romania*
[2] *Student, Medical school, Newcastle University, UK*
[3] *Institute of Oncology "Prof. Dr. Alexandru Trestioreanu", Bucharest, Romania*
[4] *"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

Corresponding author: Dan Corneliu Jinga; **e-mail**: danjinga2002@yahoo.com

Original Research

Abstract

Introduction. Cutaneous melanoma is one of the deadliest cancers, and its incidence has dramatically increased over the last 20 years. Its mortality has decreased slightly worldwide over the past 10 years, largely due to new approaches such as sentinel node biopsy and new systemic treatments.

Matherials and method. This retrospective study comprises 151 cases of cutaneous melanoma (stages 0, I, II and III) diagnosed between 2003 and 2019 in Romanian patients at a single center. It provides epidemiological information (stage at diagnosis, histological aspects, status of BRAF mutation, pattern of recurrence) and shows survival parameters associated with systemic adjuvant treatments and first and second-line therapies for recurrence.

Results. Compared to other European countries, Romanian patients with cutaneous melanomas have different characteristics: younger age (50 years median age at diagnosis), more advanced stages (70% for male and 44% for female patients), and BRAF mutation in 70% of cases. More than 50% of the patients with stages IIB, IIC and III received adjuvant IFN-α2b after complete resection. However, there were similar outcomes in terms of median disease-free survival (DFS) (33.46 months for the entire cohort) independently of adjuvant systemic treatments administered in the interferon alpha-2b era. The 3-year DFS and OS rates for stages IIB and IIC were similar to those of stage III. The prognosis was worse for BRAF mutated melanoma in terms of DFS and OS, independently of clinical stages.

Conclusion. Our study demonstrates that stages IIB and IIC have the same pattern of recurrence and similar outcomes to those of stage III and could benefit from adjuvant systemic treatment as shown in KEYNOTE-716 clinical study.

Keywords: *early and advanced cutaneous melanoma; adjuvant interferon alpha-2b therapy; BRAF mutation; BRAF inhibitors and MEK inhibitors; PD-1 inhibitors; dual immune blockade*

https://doi.org/10.53011/JMRO.2022.01.06

1. Introduction

Cutaneous melanoma is a deadly cancer whose incidence has increased dramatically over the last 20 years (1). In 2020, more than 320.000 melanomas were diagnosed worldwide, half of which were in Europe. The global prevalence was greater than 1 million cases (2).

Melanoma management has changed significantly since the introduction of sentinel lymph node biopsy and systemic innovative therapies like targeted therapy (TT) with BRAF inhibitors (BRAFi) and MEK inhibitors (MEKi), as well as immune therapy (IT) based on immune checkpoint inhibitors (ICI). These changes are correlated with decreased mortality rates over the past 10 years (3), with only 57,000 worldwide deaths in 2020 (2). Nevertheless, half of the diagnosed cases were in Europe (2). Romania had a low incidence rate compared to other European countries (only 1,500 new cases diagnosed in 2020), but a large number of deaths (500 deaths in 2020) (2).

For over 15 years, adjuvant therapy was limited to interferon-alpha-2b (IFN-α2b), which has good disease-free survival rates but clinically significant adverse events, especially for high-dose therapy (HD- IFN-α2b), and questionable overall survival improvements (4). In accordance with Romanian national guidelines, we administered low dose interferon (LD-IFN-α2b) for 1 to 3 years, or HD- IFN-α2b with a one-month induction phase and 11-month maintenance phase.

This 15-year retrospective study reflects our experience with the diagnosis and treatment of cutaneous melanomas and is the first Romanian study that publishes real-world data from a long follow-up period of this solid tumor.

2. Material and methods

A database of 450 melanomas diagnosed over more than 20 years was used. Researchers excluded patients without complete records, with mucosal melanomas or metastatic disease, and cases diagnosed after 2019. Our study comprises 151 stage 0, I, II and III cutaneous melanomas diagnosed between 2003 and 2019. All cases were restaged using the 8th edition of AJCC melanoma staging (5) to homogenize cases diagnosed before and after 2017, when the staging was changed.

All patients were treated according to national and European guidelines. Breslow Index (BI) from a previous biopsy guided surgical excision of the primary tumor. Sentinel lymph node biopsy was performed for all cases with BI between 1-3.99 mm and was followed by dissection of regional lymph nodes for positive sentinel lymph nodes. For clinically positive stage III lymph nodes, complete lymph node dissection was performed simultaneously with the excision of the primary tumor. Patients with stage IIB, IIC and III received adjuvant systemic therapy according to national guidelines and depending on co-morbidities and patient preference.

Disease recurrence was treated with surgery (for local and regional recurrences or for oligometastatic visceral disease) and systemic treatments i.e. chemotherapy and/or innovative treatments such as targeted and immune therapy.

The first goal of this study was to determine median disease-free survival (DFS), median overall survival (OS) and 1-year, 2-year, and 3-year DFS and OS rates. The second goal was to establish the pattern of recurrence. DFS was defined as the interval from diagnosis to first recurrence (local, regional, distant metastasis or second primary cancer) and OS as the interval from diagnosis until patient death from or independently of melanoma.

3. Results

Of the 151 patients with cutaneous melanoma, 67 (44%) were early-stage (0 to IIA) and 84 (56%) were advanced-stage (IIB, IIC and III) (see Table 1). Median age at diagnosis was approximatively 50 years. Median age was 46 years for early stages and 53 years for advanced melanomas.

70% of patients were women and approximately 30% were men. Early stages were diagnosed predominantly in women (56%) and advanced stages were diagnosed predominantly in men (70%) (see Table 1).

More than half of the cases (54%) were observed on the arms, 34% on the trunk, and 12% on the scalp, face, and neck.

Table 1: Base-line characteristics of the study population with cutaneous melanoma

Stage		Stage 0-IIA	Stage IIB, IIC	Stage III	Total
Number (%)		67 (44.37%)	52 (34.43%)	32 (21.20%)	151 (100%)
Median age at diagnosis (years)		46.44 (15-79)	52.59 (18-80)	54.75 (29-69)	50.23 (15-80)
Sex	**Female**	47 (55.95%)	25 (48.07%)	12 (37.5%)	84 (70.15%)
	Male	20 (29.85%)	27 (51.93%)	20 (62.5%)	67 (29.85%)
Region	**scalp, head, neck and face**	5	11	2	18 (11.92%)
	trunck	25	16	10	51 (33.77%)
	arm	37	24	20	81 (53.64%)
	uknown	0	1 (1.93%)	0	1 (0.67%)
BRAF	**mutated**	13	17	17	47 (69.11%)
	wilde-type	8	10	3	21 (30.89%)
	uknown	46	25	12	83
median BI (mm)		1.06 (0.1-4)	4.47 (0.1-11.25)	4.03 (0.1-23.30)	2.81 (0.1-23.30)
BI (mm)	**0.1-0.79**	29	0	2	31 (20.53%)
	0.8-0.99	4	0	1	5 (3.32%)
	1-1.99	28	0	5	33 (21.85%)
	2-3.99	4	33	9	36 (23.84%)
	≥ 4	1	27	10	38 (25.16%
	uknown	1	2	5	8 (5.30%)
Ulceration	**absent**	49	3	7	59 (40.97%)
	present	17	48	20	85 (59.02%)
	uknown	1	1	5	7
Regional Lymph Nodes	**Sentinel biopsy**	13	11	15	39
	complete excision	3	5	16	24
Adjuvant treatment	**Yes**	10	27	17	54
	No	53	25	15	93
	uknown	4	0	0	4
Recurrence of disease	**Yes**	21	33	21	75
	No	46	19	11	76 (50.33%)
Median DFS (months)		52.5 (10-127)	28.84 (1-172)	20.76 (0-93)	33.46 (0-172)
Outcome	**Death**	13	20	14	47 (31.13%)
	A life	54	32	18	104 (68.87%)

45% of specimens were tested for BRAF mutations; 70% of them had a mutation on V600 and 30% were wild type. Testing was generally performed at time of recurrence. From 2018 onward, all stage III cases were tested from diagnosis.

The median BI was 2.81 mm. 25% of cases were under 1 mm, 45% were between 1

and 3.99 mm, and over 25% of cases had a BI above 4 mm (see Table 1). 60% of biopsy specimens had histological ulceration.

75% of cases (63 out of 84 patients) with stages IIB, IIC and III had a surgical staging of the disease by sentinel lymph node biopsy (39 patients) and lymph node dissection (24 patients).

54 patients received systemic adjuvant therapy, which varied by clinical stage (see Table 1).

Most treated patients received IFN-ɑ2b (see Table 2). Doses (high versus low) and duration of treatment (1 year for HD-IFN-ɑ2b and between 1 to 3 years for LD-IFN-ɑ2b) varied according to the changes in national guidelines between 2003 and 2019. Administration of IFN-ɑ2b stopped in 2017 and was replaced with innovative treatments after 2019, but only for stage III melanoma. We did not include the number of definitive stops of treatment in our database, but more than 50% patients did not tolerate systemic adjuvant therapy, especially the 1-month induction phase of the high-dose IFN-ɑ2b. Temporary and definitive stops of treatment occurred due to medullar toxicities (severe thrombocytopenia, febrile neutropenia episodes) or severe pyrexia and flu-like symptoms that impaired daily life.

Table 2: Adjuvant systemic treatment for different melanoma stages

Stage		**Stages 0-IIA**	**Stages IIB, IIC**	**Stage III**	**Stages 0, I, II, III**
Number / %		67	52	32	151
Adjuvant treatment	**IFN alpha2b**	9	22	12	43
	chemo	0	0	1	1
	BRAFi + MEKi	0	1	1	2
	PD-1	0	1	2	3
	uknown	5	3	1	9
No adjuvant treament		53	25	15	93

Table 3: 1-year, 2-year and 3-year DFS and OS rates for different melanoma stages

PFS (months)	**Stages 0-IIA (%)**	**Stages IIB, IIC (%)**	**Stages III (%)**	**Stages 0, I, II, III (%)**
1-year	98.5	84.61	68.75	87.41
2-year	91.04	69.23	53.12	75.49
3-year	89.55	57.69	46.87	69.53
OS (months)	**Stages 0-IIA (%)**	**Stages IIB, IIC (%)**	**Stages III (%)**	**Stages 0, I, II, III (%)**
1-year	98.5	96.15	84.37	95.36
2-year	97	82.69	71.87	86.75
3-year	83.58	57.69	56.25	73.75

Approximatively 50% of patients experienced recurrence; the rates for stages IIB, IIC and III (63-65%) were double that of early stages 0 to IIA (31%). The median DFS was 33.46 months for the entire study population and varied by clinical stage: 52.5 months for stages 0 to IIA, 28.84 months for stages IIB and IIC, and 20.76 months for stage III (see Table 1).

31% patients from our cohort died, the majority of which were initially diagnosed with advanced melanomas.

The 1-year, 2-year, and 3-year DFS and OS rates for the study population were

calculated. After a minimum 3-year follow up period, the OS and DFS rates for stages IIB and IIC were similar to those of stage III, with small differences in PFS (see Table 3).

We identified 4 separate major patterns of recurrence: local, regional, and bone recurrence (41% of patients experienced a recurrence); visceral metastasis (43%); brain metastasis (12%); and second cancer (3 cases: 1 melanoma, 1 colon cancer and 1 breast cancer) (see Table 4).

Table 4: Pattern of recurrence

Pattern of recurrence	Number (%)
local, regional	31 (41.33)
visceral metastasis	32 (42.66)
brain metastasis	9 (12)
second cancer	3 (4.01)
Total	**75 (100)**

Discussion

Median age at diagnosis in this study (50 years) was slightly lower compared to other studies, which report median ages of 54 (6) and 59 (7). The number of advanced melanomas was significantly higher compared to other studies (more than 50% versus under 25%) (6). It is notable that in our population, young women were diagnosed predominantly with early stages, and older men were diagnosed predominantly with advanced stages of cancer.

The median BI was 2.81 mm (see Table 1). Compared to an Italian study, fewer patients had a BI under 1mm (24% versus 60%), and more ulceration (60% versus under 20%) was observed (6).

We also identified a high number of patients with mutated BRAF melanoma (70% of 68 patients tested). The specimens were tested at the moment recurrence was diagnosed. This result is slightly different from other studies that show a 50% probability of having BRAF mutation in melanomas (8).

Approximatively 50% of patients with stages IIB, IIC and III received adjuvant systemic therapy after complete excision of the primary tumor and lymph node staging due to poor compliance with old treatments like HD-IFN-ɑ2b and chemotherapy. The lack of information about doses, duration of treatment, and temporary and definitive stops of treatment in our database did not allow us to draw conclusions about the impact of these parameters on patient outcomes.

For over 15 years, interferon alpha-2b was the only treatment approved for adjuvant therapy of stages IIB, IIC and III in Romania. After 2018, modern therapies were implemented: 2 patients from our cohort received adjuvant BRAFi combined with MEKi, and 3 patients received anti-PD-1 immune checkpoints inhibitors.

50% of patients from the cohort experienced recurrence; the median DFS was 33.46 months. Prognosis for stages IIB, IIC (median DFS 28.84 months), and III (median DFS 20.76 months) was worse than that of early stages 0 to IIA (median DFS 52.5 months). A slight difference in recurrence was observed for stages IIB, IIC and III at 3 years from diagnosis (9,1%). The Kaplan Meier disease-free survival curves by adjuvant treatment indicate the same pattern of recurrence for both clinical groups regardless of whether adjuvant treatment was administered (see Figure 1).

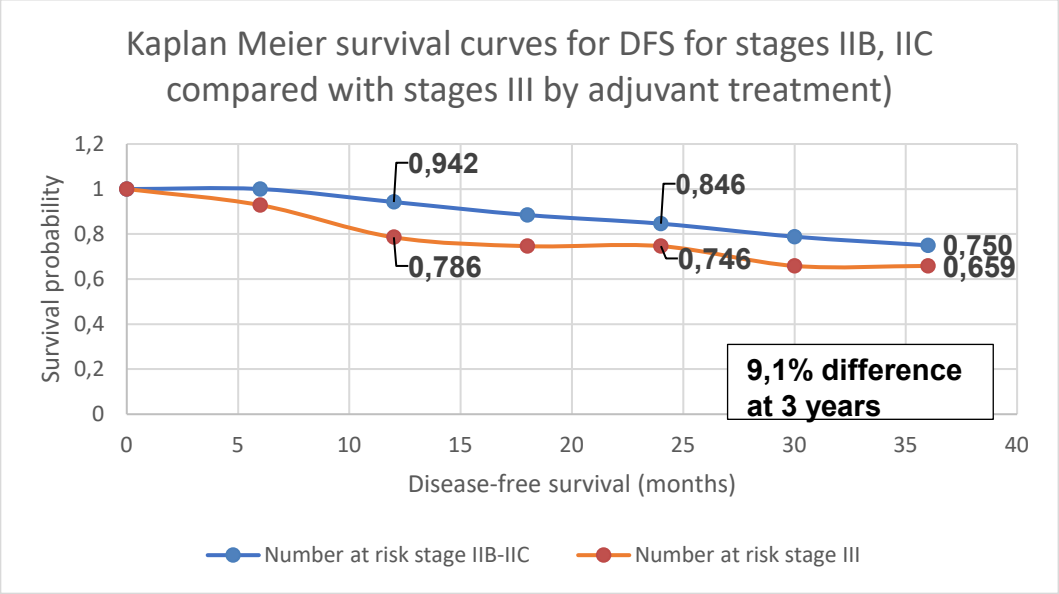


Figure 1: Kaplan Meier disease-free survival curves for stages IIB, IIC compared with stages III, by adjuvant treatment (9,1% difference at 3 years between stages IIB, IIC compared with stages III – not statistically significant)

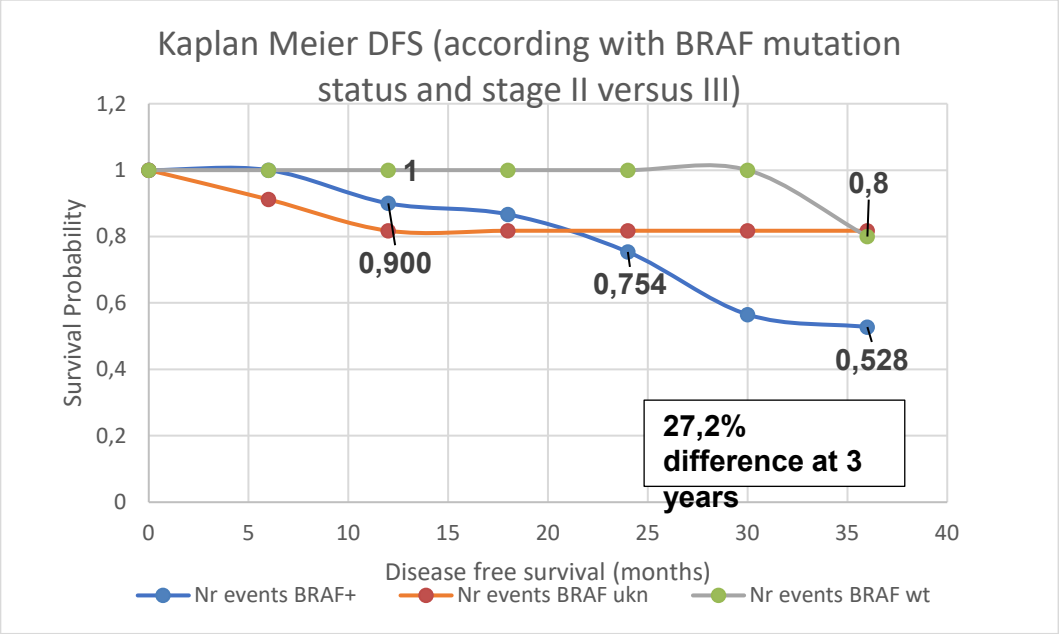


Figure 2: Kaplan Meier disease-free survival curves for BRAF mutated melanoma and unknown compared with BRAF wild-type melanomas, by stages IIB, IIC and III (27,2% difference at 3 years between BRAF mutated and unknown BRAF status melanoma and BRAF wild-type melanomas).

A 2018 meta-analysis of 13 trials showed a median relapse-free survival of 2.2 years (1,2 – 3.3 years) for patients that received different IFN-ą2b regimens and 1.9 months for patients that did not receive treatment for stages II and III, very similar with our results (9).

A large difference, statistically significant, at 3 years from diagnosis (27.2%) was observed in Kaplan Meier disease-free survival curves for BRAF mutated and unknown BRAF status melanomas versus wild-type melanomas by stages IIB, IIC, and III (Figure 2).

Outcomes for stages IIB, IIC, and III were similar, and worse than those of early stages, with approximately 40% deceased patients for both subgroups (see Table 1). The Kaplan Meier overall survival curves demonstrate a 7.3% difference (not statistically significant) between stages IIB and IIC vs. stage III, by adjuvant treatment (Figure 3) and a 19.2% difference between BRAF mutated and unknown BRAF status melanomas compared with BRAF wild-type melanomas, by stages IIB, IIC and III (Figure 4).

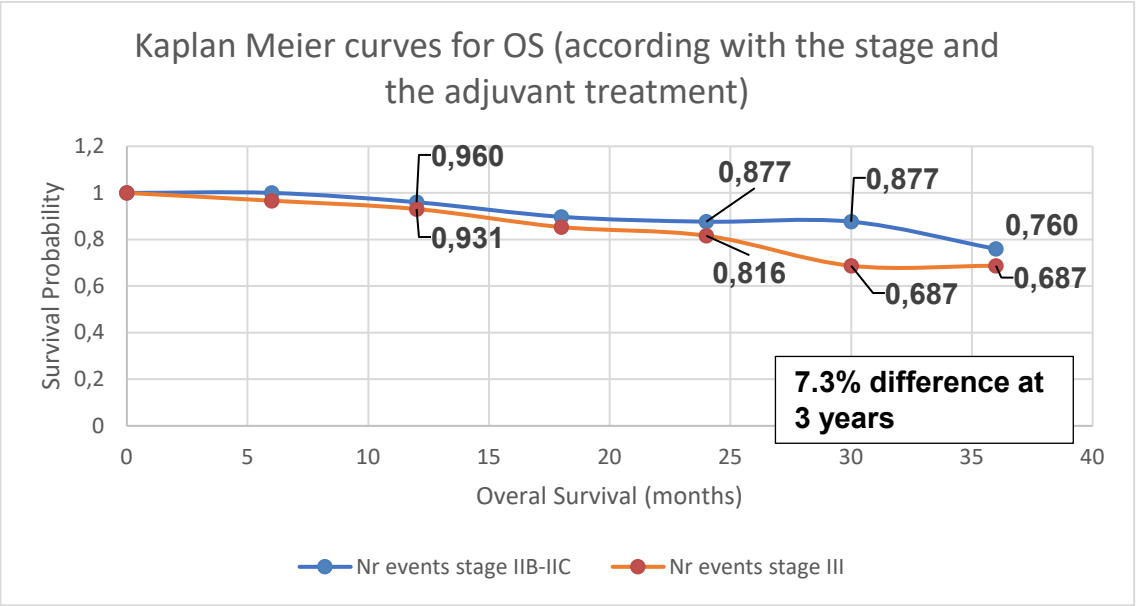


Figure 3: Kaplan Meier overal survival curves for stages IIB, IIC compared with stages III, by adjuvant treatment (7.3% difference at 3 years between stages IIB, IIC compared with stages III – not statistically sugnificant)

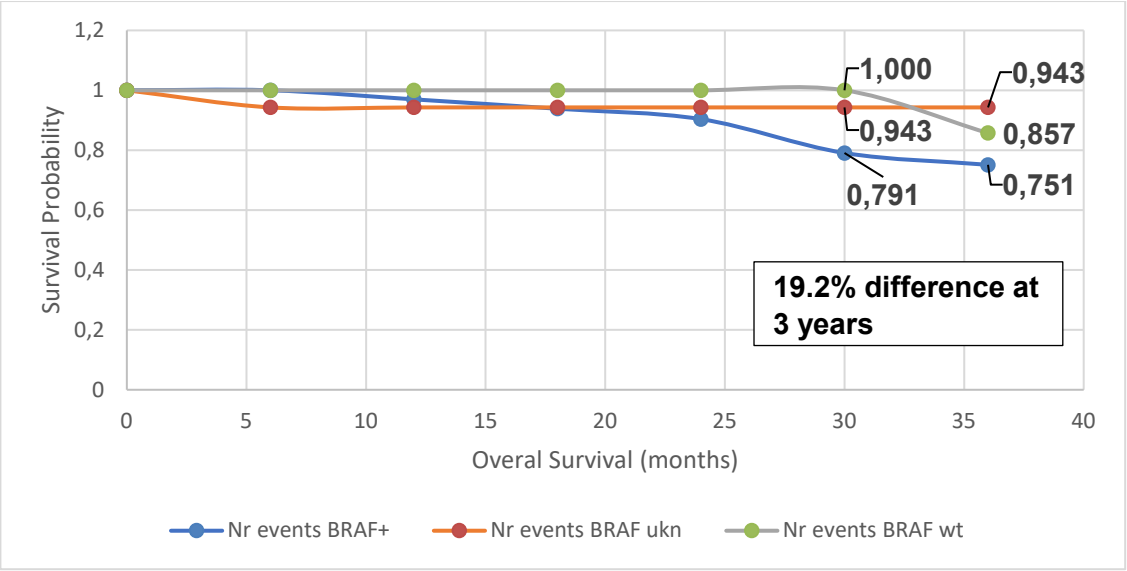


Figure 4: Kaplan Meier overal survival curves for BRAF mutated melanoma and unknown compared with BRAF wild-type melanomas, by stages IIB, IIC and III (19,1% difference at 3 years between BRAF mutated and unknown BRAF status melanoma and BRAF wild-type melanomas).

Our study demonstrates a statistically significant difference between the prognosis of BRAF mutated and BRAF wild-type melanomas, where BRAF mutated is associated with worse prognosis. These results are in accordance with a large meta-analysis using data from 52 studies, representing more than 7500 melanoma patients (10). At the moment of recurrence, targeted therapy or immune therapy was given to 42 of 66 patients (68%) as first-line treatment, and to 23 of 35 (65%) as second-line treatment (Table 4). 27% of patients are alive at time of writing (18 of 66), 14 are on first-line therapy (9 on PD-1 inhibitors, 4 on dual immune blockade and 1 on BRAFi combined with MEKi), and 4 are on second-line therapy through sequence targeted-immune therapy (TT-IT).

The Romanian guidelines for adjuvant melanoma treatment were last changed in 2019; stage III cutaneous melanoma patients now receive adjuvant immune therapy with PD-1 inhibitors, pembrolizumab or nivolumab for BRAF mutated or wild-type melanomas, and targeted therapy with BRAFi, dabrafenib, and MEKi trametinib is reserved for BRAF mutated melanomas, in accordance with National Comprehensive cancer Network (NCCN) (11) and European Society Medical Oncology (ESMO) guidelines (12).

Our findings demonstrate that both subgroups (stages IIB and IIC, stage III) experience a strikingly similar pattern of recurrence and risk of death. This similarity underlines the importance of expanding adjuvant treatment options for stage III to also treat stages IIB and IIC. Recently, NCCN guidelines introduced adjuvant treatment with pembrolizumab for stages IIB and IIC, with a similar 12-month regimen already used for adjuvant treatment of stages III and IV resected melanoma (11), based on KEYNOTE-716 clinical study results (13).

We hope that these innovative treatments will soon be available for our patients with stage IIB and IIC cutaneous melanomas.

5. Conclusion

Our retrospective clinical study is the first Romanian study to publish data that reflects the experience of one center over 15 years. It offers epidemiological information about Romanian patients (stage at diagnosis, histological aspects, status of BRAF mutation, pattern of recurrence) and important survival information associated with systemic adjuvant treatments and first and second-line therapies for recurrence.

Abbreviations:
BI - Breslow Index
BRAFi - BRAF inhibitors
DFS - disease-free survival
HD - high-dose
IFN-α2b - interferon-alpha-2b
LD – low dose
MEKi - MEK inhibitors
NCCN - National Comprehensive cancer Network
OS - overall survival
TT-IT - targeted-immune therapy

Statements:
Authors' contributions: All co-authors equally contributed to the manuscript.
Consent for publication: As the corresponding author, I confirm that the manuscript has been read and approved for submission by all co-authors.

Conflict of interest: All authors declare having no competing interests associated with this publication.

Funding Sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

Informed Consent: The informed consent was obtained from the patients treated after 2017 according to the GDPR laws. No materials which could lead to patient identification were published.

Ethical Approval: The treatment strategy was approved by a local tumor board.

References:

1. Jemal A, Saraiya M, Patel P, Cherala SS, Barnholtz-Sloan J et al Recent trends in cutaneous melanoma incidence and death rates in the United States, 1992-2006. J Am Acad Dermatol. 2011 Nov;65(5 Suppl 1):S17-25.

2. International Agency for Research on Cancer and WHO - Global Cancer Observatory https://gco.iarc.fr/

3. Henley SJ, Ward EM, Scott S, Ma J, Anderson RN, et al. Annual report to the nation on the status of cancer, part I: National cancer statistics. Cancer. 2020 May 15;126(10):2225-2249.

4. Kirkwood JM, Ibrahim JG, Sondak VK, Richards J, Flaherty LE, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. J Clin Oncol. 2000 Jun;18(12):2444-58.

5. Brierley JD, Gospodarowicz MK, Wittekind C (eds) (2017) TNM classification of malignant tumours, 8th edn. Chichester, JohnWiley and Sons.

6. Morgese F, Sampaolesi C, Torniai M, Conti A, Ranallo N, et al. Gender Differences and Outcomes in Melanoma Patients. Oncol Ther. 2020 Jun;8(1):103-114.

7 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016 Jan-Feb;66(1):7-30.

8. Dankner M, Rose AAN, Rajkumar S, Siegel PM, Watson IR. Classifying BRAF alterations in cancer: new rational therapeutic strategies for actionable mutations. Oncogene. 2018 Jun;37(24):3183-3199.

9. Suciu S, Eggermont AMM, Lorigan P, Kirkwood JM, Markovic SN, Garbe C, Cameron D, Kotapati S, Chen TT, Wheatley K, Ives N, de Schaetzen G, Efendi A, Buyse M. Relapse-Free Survival as a Surrogate for Overall Survival in the Evaluation of Stage II-III Melanoma Adjuvant Therapy. J Natl Cancer Inst. 2018 Jan 1;110(1).

10. L. Ny, M. Hernberg, M. Nyakas, J. Koivunen, L. Oddershede, M. Yoon, X. Wang, P. Guyot & J. Geisler (2020) BRAF mutational status as a prognostic marker for survival in malignant melanoma: a systematic review and meta-analysis, Acta Oncologica, 59:7, 833-844,

11. NCCN: Melanoma: cutaneous; version 3.2022; April 11, 2022; https://www.nccn.org/

12. O. Michielin, A. C. J. van Akkooi, P. A. Ascierto, R. Dummer & U. Keilholz, on behalf of the ESMO Guidelines Committee Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Annals of Oncology 30: 1884–1901, 2019.

13. Luke JJ, Ascierto PA, Carlino MS, Gershenwald JE, Grob JJ, Hauschild A, Kirkwood JM, Long GV, Mohr P, Robert C, Ross M, Scolyer RA, Yoon CH, Poklepovic A, Rutkowski P, Anderson JR, Ahsan S, Ibrahim N, M Eggermont AM. KEYNOTE-716: Phase III study of adjuvant pembrolizumab versus placebo in resected high-risk stage II melanoma. Future Oncol. 2020 Jan;16(3):4429-4438.

JMRO

Journal of Medical and Radiation Oncology

Journal homepage: www.jmedradonc.org

High-Grade Urothelial Carcinoma with Squamous Differentiation and Favourable Response to Immunotherapy – a Case Report

Alecsandra Gorzo[1], Diana Galos[1], Daniel Sur[1,2,], Ramona Matei[3]

[1] *Department of Medical Oncology, "Ion Chiricuță" Oncology Institute, Cluj-Napoca, Romania*
[2] *11th Department of Medical Oncology, University of Medicine and Pharmacy, "Iuliu Hațieganu" Cluj-Napoca, Romania*
[3] *Municipal Clinical Hospital, Cluj-Napoca, Romania*

Corresponding author: Daniel Sur; **e-mail**: dr.geni@yahoo.co.uk

Abstract

Bladder cancer is the 10th most common cancer type worldwide, with a median age of diagnostic of 75 years. Male sex, white race, personal history of pelvic radiation, and tobacco use are considered risk factors. Urothelial carcinoma (UC) is the most frequent histology. Squamous differentiation (SD) is the most common histologic variant in bladder cancer (20% of cases) and is associated with a worse prognosis. We presented the case of a 75-years old male patient diagnosed with high-grade (G3) UC of the bladder with SD who developed skin metastasis shortly after completing the adjuvant chemotherapy. He was started on immunotherapy with Atezolizumab, with good response until this report was written (for twelve months).

Keywords: *bladder cancer, squamous differentiation, skin metastasis, immunotherapy*

Clinical Case Reports

1. Introduction

Bladder cancer (BC) carries a significant social burden, with up to 550,000 cases diagnosed every year worldwide and a median age of diagnostic of 75 years (1). Tobacco use is the most common risk factor and contributes to the increasing incidence of BC in Western countries. Male sex, white race, personal history of pelvic radiationare also considered risk factors (2). BC represents a spectrum of diseases which include non-muscle-invasive disease (NMIBC), muscle-invasive disease (MIBC), and advanced or metastatic disease (3). Urothelial carcinoma (UC) is the predominant histological subtype in Europe and the United States (90%). UC with squamous differentiation (SD) is the most common histologic variant in BC (20% of cases), and it was associated with a poor

https://doi.org/10.53011/JMRO.2022.01.07
2784 – 0131/Copyright 2022 The Author(s).

prognosis (4).We presented a case of ahigh-grade(G3) UC with SD and with favourable response to immunotherapy.

2. Case Report

A 75-year-old male patient presented to our unit with a recent diagnosis of BC. The patient has a medical history of hypertension and type 2 diabetes. He did not report tobacco or alcohol use.

At the end of January 2020, the patient presented to another urology department with hematuria. A CT-urography revealed a bladder tumor measuring 45/30 mm that involved the left ureteral orifice and hydronephrosis grade 4 in the left kidney, with no abdominal or pelvic lymph nodes. Further, the patient underwent transurethral resection for bladder tumor (TURBT), in February 2020. The pathology report described a high-grade (G3) papillary UC, pT2 - MIBC. Soon after the diagnosis, at the beginning of March 2020, the patient presented to our emergency department with gross hematuria and clots. He was admitted to the urology department and stabilized. During admission, a cystoscopy was performed, which excluded an early relapse. Moreover, a CT scan of the thorax to complete the staging evaluation showed no signs of metastatic lesions. The case was further discussed in our multidisciplinary team, and the final diagnostic was of high-grade (G3) UC of the bladder T2N0M0, stage II, according to the AJCC 8th edition. Based on the stage, patient's fitness, and informed consent, the therapeutic strategy consisted of neoadjuvant chemotherapy followed by radical cystectomy. Considering the worldwide health crisis caused by the COVID-19 pandemic, which spread quickly to our country, we decided to start the treatment as soon as possible. Therefore, from March 2020 to May 2020, the patients received three cycles of neoadjuvant chemotherapy based on carboplatin AUC5 and gemcitabine 1000 mg/m2. After completing the three cycles, the CT scan described the bladder having diffuse wall thickening (12 mm) and multiple diverticula, hydronephrosis grade 2/3 in the left kidney, and iliac lymph nodes measuring about 8-10 mm in short axis diameter. (Fig. 1).

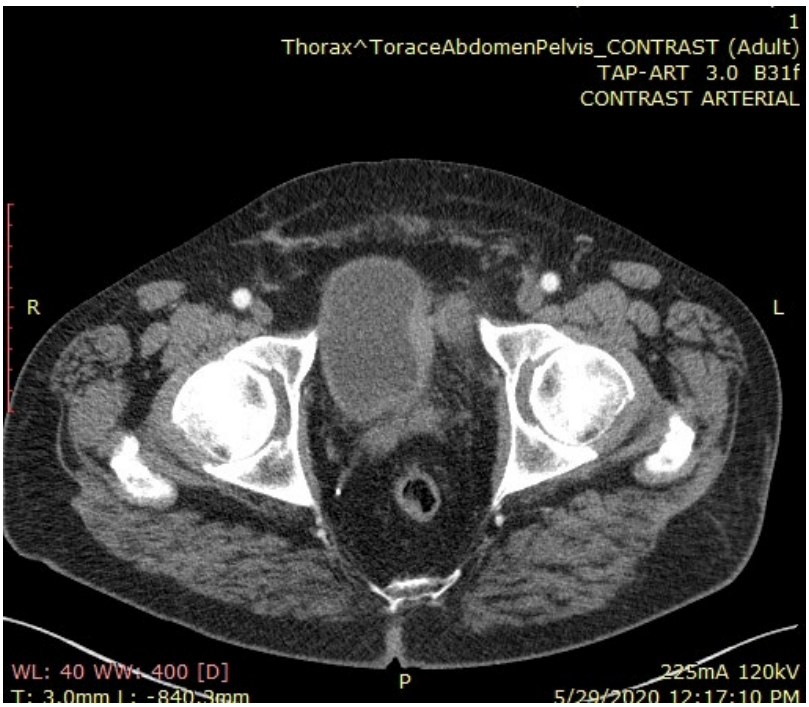


Fig.1: CT scan after neoadjuvant chemotherapy

Consequently, in June 2020, the patients underwent cystoprostatectomy, and the pathology report revealed a high-grade UC (G3) with SD (20%) ypT3aN1MxL1VoPnoRo. Considering the poor prognostic factors (squamous differentiation, residual disease after neoadjuvant therapy, lymphovascular invasion), we decided to complete the therapeutic sequence with adjuvant chemotherapy. Therefore, from August 2020 to October 2020, the patients received three additional cycles of adjuvant chemotherapy with carboplatin AUC5 and gemcitabine 1000 mg/m^2.

Shortly after completing the treatment, in December 2020, the patient presented with indurated skin nodules in the hypogastrium at the surgical incision site. The lesions were interpreted as skin metastasis (Fig. 2).

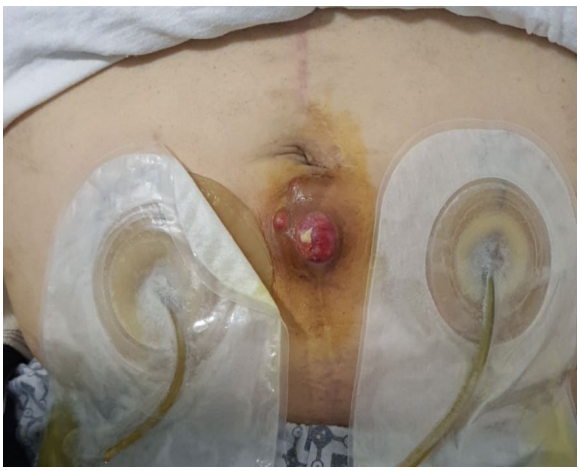


Fig. 2: Erythematous, indurated skin nodules in the hypogastrium

A CT scan confirmed the recurrence. The results showed a soft tissue mass in the lower anterior abdominal wall measuring 3/4 cm and another with similar characteristics in the lower right anterolateral wall. Moreover, the CT scan showed a left iliac lymphadenopathy measuring 3.5/2 cm and peritoneal carcinomatosis. Considering the available treatment options, from January 2021, the patient was started on immunotherapy with Atezolizumab 1200mg IV every 3 weeks. The first follow-up CT scan was performed after three months, in March 2021 and pelvic lymph nodes measured less than 10mm in diameter. The patient maintained a good performance status (IP ECOG 1), no adverse events were reported throughout treatment, and the skin nodules were considerably reduced in size (Fig. 3).

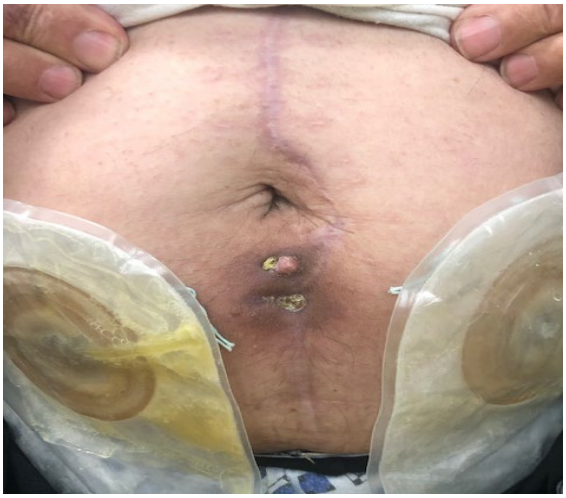


Fig. 3: Clinical assessment after three months of immunotherapy- skin nodules reduced in size

Systemic therapy was maintained with Atezolizumab 1200 mg IV 3 weeks. Subsequent clinical and imagistic follow-up showed overall improvements, and the systemic immunotherapy was continued until this report was written (Fig.4).

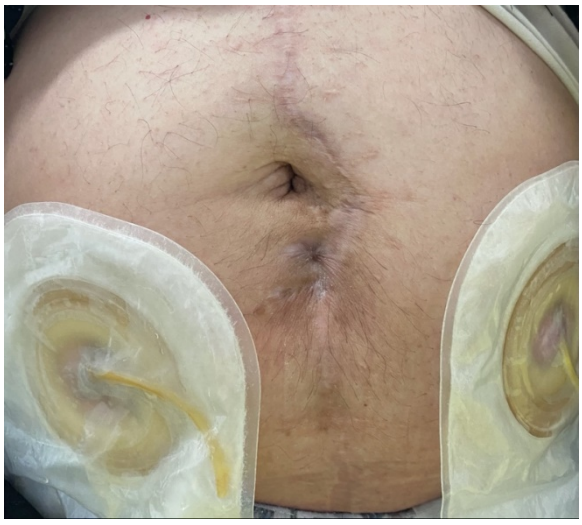


Fig. 4: Clinical assessment from December 2021

3. Discussion

UC is the most common tumor type of the urinary tract and has a propensity for divergent differentiation. Squamous differentiation occurs in about 20% of cases and is characterized by intracellular bridges of keratinization (5). This histological variant was associated with more advanced stages, shorter disease-free survival (DFS), and a higher recurrence rate (RR) (6). As regards our case, recurrence was diagnosed very shortly after completing the adjuvant sequence, after only two months. In terms of overall survival (OS), the data are inconsistent. However, SD did not significantly influence OS in a recent meta-analysis investigating its prognostic value (7).

BC represents a spectrum of diseases which NMIBC, MIBC, and metastatic disease (8). The most common metastatic sites are regional lymph nodes, lung, liver, and bone. Skin metastasis is a rarity, with a handful of cases reported in the literature till now. The overall incidence of cutaneous metastasis is about 5% for all malignancies and 0.8% for BC (9). Skin infiltration by cancerous cells can occur through several routes, including lymphatic, hematologic, iatrogenic implantation, or direct tumor invasion. In our case, iatrogenic implantation following an extensive surgery like cystoprostatectomy could the underlying mechanism leading to skin metastasis. Moreover, the lesions can mimic other dermatological conditions like melanoma or sarcoma (10).

The treatment of BC was almost unchanged during the last three decades. BC was one of the most underfunded among the common cancer types in the early 2000s, which limited the understanding of tumor biology and led to inadequate treatment progress (11). The mixed histologies, including SD, are usually treated in the same manner as pure UC. On the other hand, pure squamous cell carcinoma and adenocarcinoma were not proven to benefit from neoadjuvant/adjuvant chemotherapy.Our patient presented with the diagnostic of MIBC, for which the standard of care consists of radical cystectomy. The high RR following radical cystectomy alone pointed to the use of neoadjuvant chemotherapy (cisplatin-based regimens) (12). However, our patient presented with kidney function impairment (creatinine clearance-43 ml/ min/ 1.73mp), and therefore cisplatin was replaced with carboplatin.The role of adjuvant chemotherapy remains a matter of debate, especially in patients who previously received neoadjuvant chemotherapy. Adequately powered randomized control trials did not fully establish its' role (13). Though, observational studies reported a survival benefit associated with adjuvant chemotherapy after neoadjuvant treatment and radical cystectomy, especially in patients with adverse pathologic features (pT3/ T4 and/or pN+) (14). Therefore, considering the poor prognostic factors after radical cystectomy (squamous differentiation, residual disease after neoadjuvant therapy, lymphovascular invasion), we proposed three cycles of adjuvant chemotherapy to our patient.

As regards the metastatic setting, an initial cisplatin-based regimen is the preferred treatment option (15). In 2016, atezolizumab (a PD-L1 inhibitor) was the first new drug approved by the FDA in more than 20 years to treat advanced/metastatic UC who progressed after platinum-based chemotherapy (16). However, in the long-term analysis of the phase III IMvigor211 trial, atezolizumab did not confer an OS benefit compared to chemotherapy in prior-platinum-treated advanced/metastatic UC patients. Consequently, these results led to the withdrawal of atezolizumab for this indication as second-line therapy in the United States.Currently, there are five immune checkpoint inhibitors (ICIs) approved for the treatment of advanced UC (atezolizumab, pembrolizumab, nivolumab, durvalumab, and avelumab) (17). Recently, atezolizumab and pembrolizumab received approval as first line in cisplatin-ineligible patients with advanced UC (18).The clinical efficacy of ICIs in tumors with predominant or pure variant histologies was poorly understood, as these categories were kept out from clinical trials. Recent studies brought light into the subject and showed that histological variants, including squamous differentiation, have comparable rates of PD-L1 expression with those found in urothelial tumors. These findings suggest that histological variants could benefit from ICIs as much as pure UC.

Metastatic bladder cancer has a poor prognosis with a 5-year OS of 5%. Moreover, skin metastasis from a primary UC is associated with a median OS of less than a year (19). Our patient received immunotherapy for twelve months with no sign of disease progression and no adverse events reported. (Fig. 4)

4. Conclusion

The occurrence of UC with SD is rare and may reflect a poor outcome. Therefore, it is essential to diagnose the histological variants correctly to determine the optimal treatment and predict the patient's prognostic.

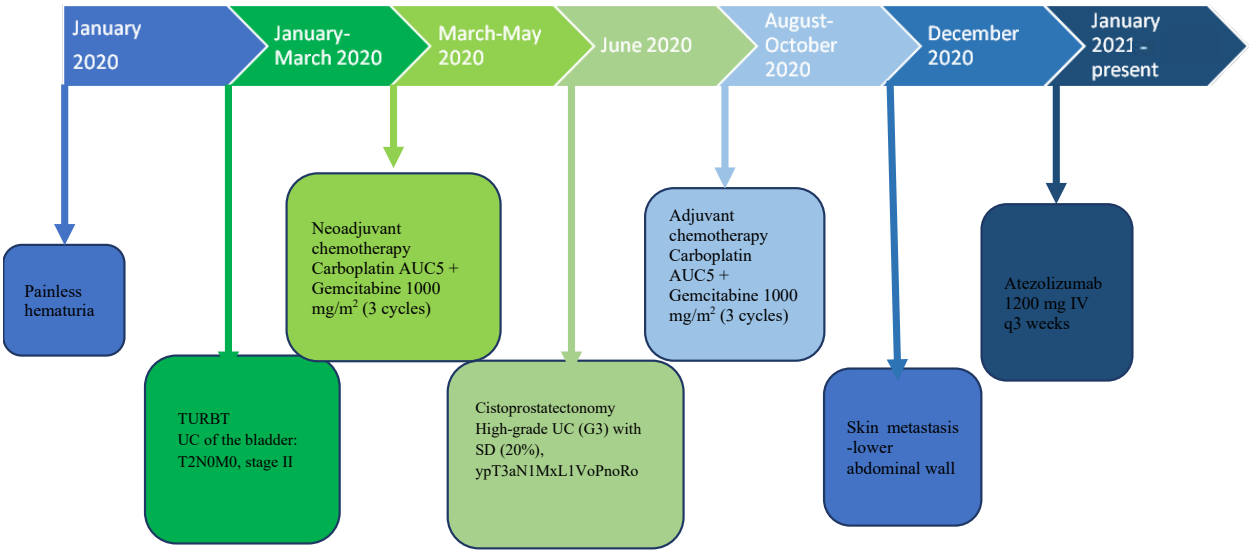


Fig. 4: The patient's disease progression and treatment options

Abbreviations:
BC - bladder cancer
DFS - disease-free survival
FDA - Food and Drug Association
ICIs - immune checkpoint inhibitors
MIBC - muscle-invasive bladder cancer
NMIBC - non-muscle invasive bladder cancer
OS - overall survival
RR - response rate
SD - squamous differentiation
TURBT - transurethral resection for bladder tumor
UC - urothelial carcinoma

Statements:
Authors' contributions: All co-authors equally contributed to the manuscript.
Consent for publication: As the corresponding author, I confirm that the manuscript has been read and approved for submission by all co-authors.
Conflict of interest: All authors declare having no competing interests associated with this publication.
Funding Sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.
Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review.

Ethical Approval: The treatment strategy was approved by the „Institute of Oncology Cluj-Napoca" tumor board.

References:

1. Richters A, Aben KKH, Kiemeney LALM. The global burden of urinary bladder cancer: an update. World J Urol 2019 388. 2019;38(8):1895–904.

2. Cumberbatch MGK, Jubber I, Black PC, Esperto F, Figueroa JD, Kamat AM, et al. Epidemiology of Bladder Cancer: A Systematic Review and Contemporary Update of Risk Factors in 2018. Eur Urol. 2018;74(6):784–95.

3. DeGeorge KC, Holt HR, Hodges SC. Bladder Cancer: Diagnosis and Treatment. Am Fam Physician. 2017;96(8):507–14.

4. Liu Y, Bui MM, Xu B. Urothelial Carcinoma with Squamous Differentiation is Associated with High Tumor Stage and Pelvic Lymph-Node Metastasis. Cancer Control. 2018;24(1):78–82.

5. A L-B, V H, R M, A C, MR R, L C. Variants and new entities of bladder cancer. Histopathology. 2019;74(1):77–96.

6. Li G, Yu J, Song H, Zhu S, Sun L, Shang Z, et al. Squamous differentiation in patients with superficial bladder urothelial carcinoma is associated with high risk of recurrence and poor survival. BMC Cancer 2017 171. 2017;17(1):1–9.

7. Lin X, Deng T, Wu S, Lin SX, Wang D, Wu C-L. The clinicopathological characteristics and prognostic value of squamous differentiation in patients with bladder urothelial carcinoma: a meta-analysis. World J Urol 2019 382. 2019;38(2):323–33.

8. Mar N, Dayyani F. Management of Urothelial Bladder Cancer in Clinical Practice: Real-World Answers to Difficult Questions. J Oncol Pract. 2019;15(8):421–8.

9. Hasan O, Houlihan M, Wymer K, Hollowell CMP, Kohler TS. Cutaneous metastasis of bladder urothelial carcinoma. Urol Case Reports. 2020;28:101066.

10. Wong CY Bin, Helm MA, Kalb RE, Helm TN, Zeitouni NC. The Presentation, Pathology, and Current Management Strategies of Cutaneous Metastasis. N Am J Med Sci. 2013;5(9):499.

11. Patel VG, Oh WK, Galsky MD. Treatment of muscle-invasive and advanced bladder cancer in 2020. CA Cancer J Clin. 2020;70(5):404–23.

12. Witjes JA, Bruins HM, Cathomas R, Compérat EM, Cowan NC, Gakis G, et al. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2020 Guidelines. Eur Urol. 2021;79(1):82–104.

13. Leow JJ, Martin-Doyle W, Rajagopal PS, Patel CG, Anderson EM, Rothman AT, et al. Adjuvant Chemotherapy for Invasive Bladder Cancer: A 2013 Updated Systematic Review and Meta-Analysis of Randomized Trials. Eur Urol. 2014;66(1):42–54.

14. Seisen T, Jamzadeh A, Leow JJ, Rouprêt M, Cole AP, Lipsitz SR, et al. Adjuvant Chemotherapy vs Observation for Patients With Adverse Pathologic Features at Radical Cystectomy Previously Treated With Neoadjuvant Chemotherapy. JAMA Oncol. 2018;4(2):225–9.

15. Witjes JA, Babjuk M, Bellmunt J, Maxim Bruins H, De Reijke TM, De Santis M, et al. EAU-ESMO Consensus Statements on the Management of Advanced and Variant Bladder Cancer—An International Collaborative Multistakeholder Effort†: Under the Auspices of the EAU-ESMO Guidelines Committees. Eur Urol. 2020;77(2):223–50.

16. Hoffman-Censits JH, Grivas P, Heijden MS Van Der, Dreicer R, Loriot Y, Retz M, et al. IMvigor 210, a phase II trial of atezolizumab (MPDL3280A) in platinum-treated locally advanced or metastatic urothelial carcinoma (mUC). J Clin Med. 2016;34(2_suppl):355–355.

17. Wołącewicz M, Hrynkiewicz R, Grywalska E, Suchojad T, Leksowski T, Roliński J, et al. Immunotherapy in Bladder Cancer: Current Methods and Future Perspectives. Cancers 2020, Vol 12, Page 1181. 2020;12(5):1181.

18. Lopez-Beltran A, Cimadamore A, Blanca A, Massari F, Vau N, Scarpelli M, et al. Immune Checkpoint Inhibitors for the Treatment of Bladder Cancer. Cancers (Basel). 2021;13(1):131.

19. SEER*Explorer [Internet]. [cited 2021 Nov 6]. Available from: https://seer.cancer.gov/explorer/

JMRO

Journal of Medical and Radiation Oncology

Journal homepage: www.jmedradonc.org

Synchronous Urinary Bladder and Gluteal Muscle Metastases of Malignant Melanoma: A Case Report and Review of the Literature

Remus Șereș[1], Dragoș Goadă[1], Andreea – Iulia Pricopie[2], Andrada Deac[1], Corina Bocșa[3], Bogdan Petruț[1,4]

[1] "Prof. Dr. Ion Chiricuţă" Oncology Institute, Cluj-Napoca, Romania
[2] Department of Biochemistry and Chemistry of environmental factors,"George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu-Mureș, România
[3] 2nd Internal Medicine Department, "Iuliu Haţieganu"University of Medicine and Pharmacy Cluj-Napoca
[4] Department of Urology, Faculty of Medicine, "Iuliu Haţieganu" University of Medicine and Pharmacy, Romania

Corresponding author: Remus Șereș; **e-mail**: seres.remus@yahoo.com

Abstract

Malignant melanoma has been known to metastasize; several cases in the literature have reported its metastasis to the urinary bladder. Metastasis to the gluteal muscle, however, is quite unusual. We report a case of malignant melanoma metastatic lesions in the urinary bladder and gluteal muscle, with a very good response to targeted therapy despite the aggressive behavior of this disease.

Keywords: *BRAF-mutation, melanoma, bladder metastasis, gluteal muscle metastasis, targeted therapy*

Clinical Case Reports

1. Introduction

Malignant melanoma is the 17th most common cancer worldwide, and is responsible for nearly 73% of skin cancer-related deaths due to its aggressive behavior (1). Melanoma-induced metastatic lesions of the bladder are extremely rare, with few reported cases (2). Skeletal muscle metastasis is also uncommon, possibly due to the large percentage of asymptomatic cases and the challenges faced in diagnosing it, as there are no specific imaging techniques for differentiating between carcinomas, sarcomas, and other muscular disorders (3).

This study presents a case of melanoma with concomitant urinary bladder and gluteal muscle metastasis. To our knowledge, there is

https://doi.org/10.53011/JMRO.2022.01.08

no similar case in the literature with this pattern of dissemination. Given the rarity of the case, we performed a literature review to obtain further information.

2. Case presentation

A 40-year-old male with no relevant medical, familial, or psychosocial history presented to the Department of Urology of a regional hospital in August 2016. The patient had been experiencing dysuria and hematuria for a month. A computed tomography (CT) scan of the abdomen and pelvis revealed a tumoral mass invading the anterior and lateral wall of the urinary bladder with no involvement of the seminal vesicles, prostate, or ureters. A cystoscopy was performed, but the patient experienced rapid worsening of symptoms. Due to the depth of malignant invasion of the bladder wall, the surgical team performed radical cystoprostatectomy with pelvic lymphadenectomy and urinary deviation, a procedure known as bilateral percutaneous ureterostomy.

The histopathological examination confirmed the diagnosis of metastasis from a malignant melanoma, which had infiltrated all layers of the bladder wall, and was associated with mucosal ulceration, serous involvement, and infiltration of the adjacent striated muscle. The mitosis index was 8 mitoses/mm2. Tumor necrosis represented approximately 30% of the tumor volume. Nine lymph nodes were resected and examined, and no tumor deposits were found. Immunostains were positive for S100, HMB-45, and Melan-A and negative for CK7, CK20, and CK8/18, BRAF V600 mutant status.

The skin of the patient was also examined, revealing a right paravertebral regressed nevus that may have represented the origin of the melanoma, which began as a prolonged ulcerative area 4 years prior.

The performed ultrasound (US) and CT scans of the abdominal and pelvic regions showed suspicious gluteal and hepatic lesions with extensive collateral vascular circulation and marked splenomegaly. These findings may have been related to a previously diagnosed portal cavernoma (Fig.1,2).

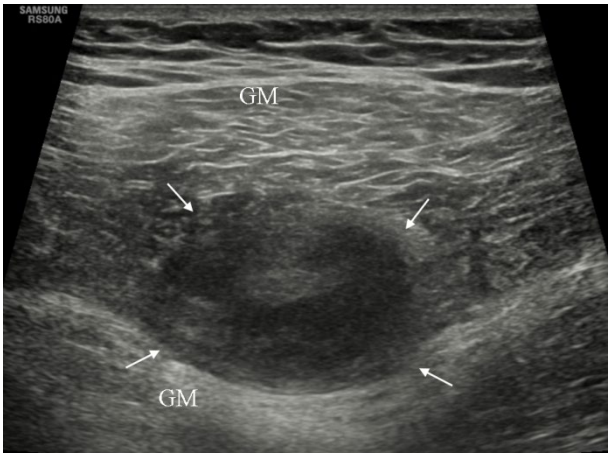


Fig.1 Right gluteal metastasis revealed by ultrasound

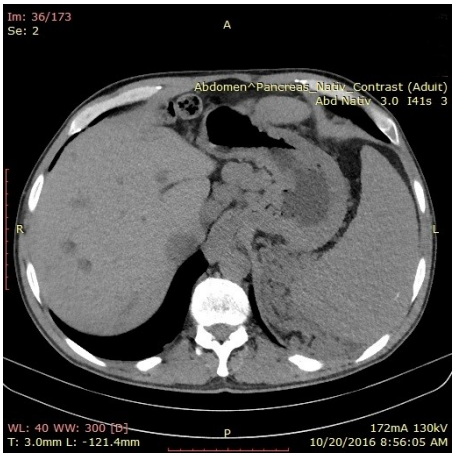


Fig. 2 Possible liver metastasis revealed by CT scan

Upon performing a fluorodeoxyglucose (FDG) positron emission tomography (PET) scan in October 2016, multiple metabolically active lesions were found: two in the left axillary region, measuring 25/20 mm and 55/35 mm respectively, with a maximum standardized uptake value (SUVmax) of 15.68, five retroperitoneal lesions, and two lesions in the right gluteal muscle, measuring 42/33 mm and 31/21 mm respectively with SUVmax of 14.34 (Fig. 3).

Unfortunately, immunotherapy and BRAF-targeted therapy were not available in Romania when treatment began.

Given the fulminant progression of the disease, systemic chemotherapy with Dacarbazin was initiated in October 2016. After 4 cycles of Dacarbazin, the patient started experiencing pain in the right lower limb. This was attributed to progression in the inguinal lymph nodes. In February 2017, the treatment was switched to Carboplatin and Paclitaxel. After two cycles, clinical progression was noted in the inguinal, axillary, and supraclavicular lymph nodes.

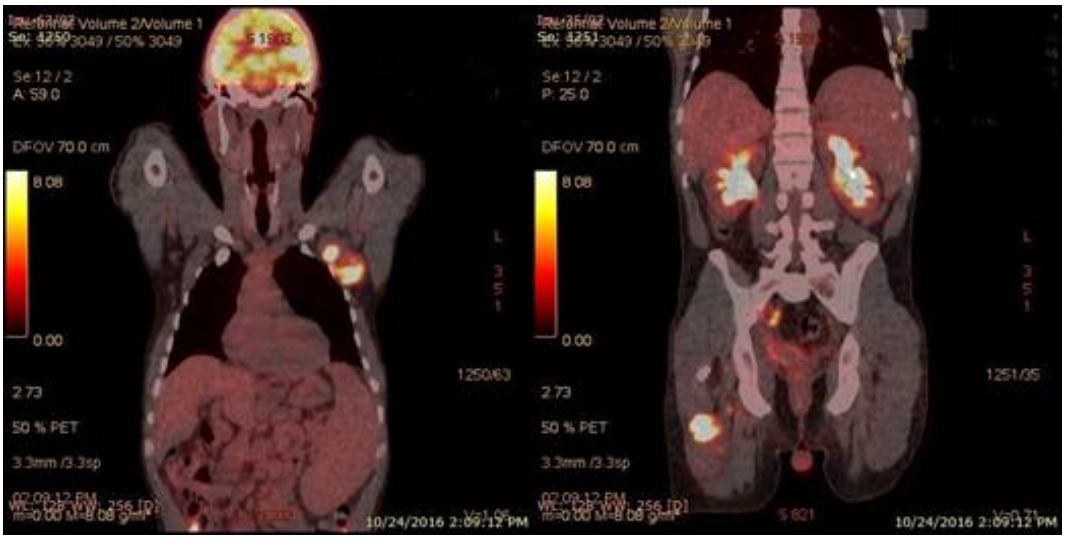


Fig. 3 Metastasis in axillary, retroperitoneal lymph node, and gluteal muscle revealed by PET scan

A molecular analysis of the tumor demonstrated a BRAF V600E mutation. In March 2017, treatment with Dabrafenib (Tafinlar) was initiated. Unfortunately, at that time only Dabrafenib was reimbursed by the patient's insurance and a MEK inhibitor (e.g. Trametinib) could not be given.

The patient was followed up with monthly clinical evaluations and lab tests. His clinical status improved and the analgesics were discontinued. The treatment with Dabrafenib was well tolerated, with minimal hematological toxicity.

Thoracic, abdominal, and pelvic CT scans were done every 6 months, and documented persistent stable disease overall. At the January 2022 assessment the axillary, mediastinal, and abdominal lymph nodes were lower than 1 cm and no other lesions were noted.

As of last follow-up, in June 2022, the patient continued to be asymptomatic, with a maintained performance status (PS) of 1. The CT scans continued to show stable disease. He is currently continuing treatment with Dabrafenib.

3. Discussion

Bladder invasion, either caused by metastatic melanoma or by melanoma developing in the bladder wall, are rare conditions which can be diagnosed almost exclusively by cystoscopy. The diagnostic is established by immunohistochemical analysis with S-100, HMB-45, and Melan-A specific antigens (4). Symptomatic bladder lesions can be resected by transurethral surgery. Partial or radical cystectomy are more aggressive approaches, and are usually performed for solitary or localized metastatic disease (5). Due to the aggressivity of this tumor, the patient was surgically treated with radical cystectomy and prostatectomy.

Compared to other similar cases reported in the literature and treated with transurethral resection (TUR)/cystectomy and that had synchronous metastases, our patient has a good PS and demonstrated a progression free survival (PFS) of almost 48 months (Table 1).

Table 1. Treatment of melanoma cases with bladder metasases

Reference	Sex/ Age	Synchronous metastasis	Treatment	Survival
Bartone (6)	F/70	Lymph nodes	Partial cystectomy	Died within 2 months
Dasgupta (7)	F/35	Axillary lesions	TUR	Died within 4 months
Meyer (8)	F/60	Lungs	TUR	Died 2 months after resection
Silverstein (9)	M/56	Lymph nodes	Intra-tumor BCG vaccine followed by partial cystectomy	Alive at 8 month follow-up
Stein (10)	M/50	Absent	TUR/chemotherapy	Alive at 2 year follow-up
Arapantoni-Dadioti (11)	F/28	Brain, lungs Lymph nodes	TUR	Died 2 months after resection
Efesoy (12)	F/60	Lungs	TUR	Died 7 months after resection
Nair (13)	M/54	Widespread including ureteral and renal pelvic	TUR and laser ablation of ureteral and renal pelvic tumors	Died within 3 months of TURBT
Shkula (14)	M/60	Widespread	TUR	Alive at 1 year follow-up

An uncommon feature of this case is the metastasis to the gluteal muscle. Metastasis to the skeletal muscle occurs only in 0.8% of patients with malignant melanoma.

Literature reports on muscle metastasis from malignant melanoma are scarce. In a retrospective cohort study that included 305 patients diagnosed with malignant melanoma, only 4 patients with skeletal muscle metastases were identified (15).

Other reports described muscle metastases from melanoma in the quadriceps, temporalis, and sartorius muscles. (16-18). Calvert and Goforth reported the presence of metastatic melanoma in the skeletal muscles of patients examined post-mortem (19). Portilla et al. reported an isolated rectus abdominis metastasis from melanoma (20). Hering et al. reported on a series of 15 patients with skeletal muscle metastases, of which only 2 of the primary tumors were melanomas. The melanomas metastasized to the gracilis and vastus lateralis, respectively (21).

It is critical to emphasize the importance of investigating the BRAF status for therapeutic purposes. Patients with tumors with BRAF mutations that received targeted therapies had better OS compared to patients treated with chemotherapy or patients that did not receive treatment (15) (Table 2).

Table 2. Skeletal metastasis from melanoma and survival depending of BRAF status

Sex/age	Metastasis site	BRAF status	Survival (months)
F/78	Toe	Wild type	11
F/56	Gluteus muscle	Wild type	4
F/53	Wing of ilium	Mutated	29
M/45	Spine	Wild type	2
F/76	Temporal bone	Wild type	2
F/38	Knee	Mutated	24

The management of metastatic melanoma is strongly dependent on the tumor's location, stage, and genetic profile. Before the introduction of immunotherapy, cytotoxic chemotherapy such as Dacarbazine and its active metabolite, Temozolomide, were the first agents used in advanced-stage melanoma.

In the immunotherapy era, chemotherapy was abandoned, as it confers only modest clinical benefit.

Inhibited T-cell functionality is a hallmark of cancer, including malignant melanoma. On their surface, the tumor cells express inhibitory molecules that down-regulate CD4+ and CD8+ lymphocyte activity, such as cytotoxic T-lymphocyte-associated antigen-4 (CTLA- 4) and Programmed Death Protein 1/ Programmed Death Protein Ligand 1 (PD-1/PD-L1). The development of specific immune checkpoint antibodies targeting PD-1, PD-L1, and CTLA-4 revolutionized the treatment of advanced-stage melanoma. The response rate and OS in metastatic melanoma were significantly increased after treatment with checkpoint inhibitors was introduced (18). Patients treated with checkpoint inhibitors have to be closely monitored because of potential autoimmune side effects.

BRAF mutations are present in approximately 40-60% of melanoma tumors. BRAF-targeted inhibitors like Dabrafenib and Vemurafenib increase the OS and PFS for patients with BRAF V600E mutations.

The clinical activity and tolerability of BRAF inhibitors administered to BRAF mutant melanoma patients was first demonstrated in the BREAK-2 phase 2 trial. In the BREAK-2 trial, 84% of patients had prior systemic treatment, and the median follow-up was 13 months. The 5- year PFS was found to be 11%.

In the BREAK-3 trial, that randomized Dabrafenib and Dacarbazine, the five-year OS was 24% for Dabrafenib and 22% for Dacarbazine. Patients in the Dacarbazine arm were allowed to switch to Dabrafenib when their disease progressed. 59% did the switch, explaining the similar 5-year OS between the two arms (24).

Lactate dehydrogenase (LDH) is a useful biomarker for assessing melanoma prognosis. The 5-year PFS in patients with normal LDH was 16% vs. 4% in those with elevated LDH in several phase 2 and 3 clinical trials (24). Long-term treatment with Dabrafenib seems to be well-tolerated. Based on the results of the COMBI-d and COMBI-v trials, the combination of Dabrafenib with Trametinib is currently the standard of care for first-line treatment of patients with sensitive BRAF mutation, leading to long-term benefit in approximately one third of patients (25). Dabrafenib is used alone only when unacceptable toxicity to Trametinib occurs.

Based on the results of the above studies, Dabrafenib should be used in combination with Trametinib. In our case, Dabrafenib was used alone, because Trametinib was not available.

4. Conclusions

We report a case of aggressive malignant melanoma with an unusual metastatic pattern involving the bladder and skeletal muscle. Remarkably, our patient demonstrated a long-term response to Dabrafenib despite the fact that the drug was started seven months after initial diagnosis and prior progression with chemotherapy. The patient continues to demonstrate stable disease more than 5 years after introducing targeted therapy.

Abbreviations:
CT - computed tomography
US - Ultrasound
FDG-PET - Fluorodeoxyglucose – positron emission tomography
SUV Ibm Max - maximum standardized uptake value lean body mass
MEK - mitogen-activated proteine kinase
CTLA – 4 - Cytotoxic T Lymphocyte Associated protein 4
PR - partial response
PS - performance status
ECOG - Eastern Cooperative Group
PFS - Progression Free Survival
PD – 1/PD-L1 - Programmed Death Protein 1/Programmed Death Protein-
Ligand 1 TUR - transurethral resection
M - male, F - female
OS - overall survival

Statements:
Authors' contributions: All co-authors equally contributed to the manuscript.
Consent for publication: As the corresponding author, I confirm that the manuscript has been read and approved for submission by all co-authors.
Conflict of interest: All authors declare having no competing interests associated with this publication.
Funding Sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.
Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review.
Ethical Approval: The treatment strategy was approved by the „Institute of Oncology Cluj-Napoca" tumor board.

References

1. Global Cancer Observatory. Melanoma of skin [Internet]. 2020 [cited 2021 Nov 27]. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/16-Melanoma-of-skin-fact-sheet.pdf

2. Kumar RA, Batra N, Frankel J, et al. Melanoma metastasis to the bladder: A case report. Urology Case Reports. 2022;40:101941

3. Paterson A, Sut M, Kaul A. Metastatic malignant melanoma of the urinary bladder: Case report and literature review. Central European Journal of Urology. 2012;65:232-234

4. Patil RV, Woldu SL, Lucas E, et al. Metastatic melanoma to the bladder: case report and review of the literature. Urol Case Rep. 2017;11:33-36

5. Viswanathan N, Khanna A. Skeletal muscle metastasis from malignant melanoma. British Journal of Plastic Surgery. 2005;58:855-858

6. BartoneFF. Metastatic melanoma of the bladder. *Journal of Urology*. 1964;91:151–155

7. Dasgupta T, Brasfield R. Metastatic melanoma. A clinicopathological study. Cancer. 1964;17:1323-1339.

8. Meyers ML, Balch CM. Diagnosis and treatment of metastatic melanoma Cutaneous melanoma, 3rd ed St. Louis: Quality Medical Publishing. 1998;325–372.

9. Silverstein MJ, DeKernion J, Morton DL. Malignant melanoma metastatic to the bladder. Regression following intratumor injection of BCG vaccine. Journal of the American Medical Association. 1974;229(6):688

10. Stein BS, Kendall AR. Malignant melanoma of the genitourinary tract. J Urol.1984;132:859-868

11. Arapantoni- Dadioti P, Panayiotides J, Kalkandi P, et al. Metastasis of malignant melanoma to a transitional cell cercinoma of the urinary bladder. European Journal of SurgicalOncology. 1995;21

12. Efesoy O,Cayan S.Bladdermetastasis of malignant melanoma: a case report and review of literature. Med Oncol. 2011;28:667-669

13. Nair BC, Williams NC, Cui C, Summers D, et al.Conjunctival Melanoma: Bladder and Upper Urinary Tract Metastases . Journal of ClinicalOncology. 2011;29(9)

14. Shukla A,Wingate JT,Baker KC, et al. HexaminolevulinateBlue-LightCystoscopy in a Patientwith Metastatic Melanoma of the Bladder. Journal of Endourology Case Reports. 2016;2:68-70

15. Nieves Gómez-Leóna, Vilma Pacheco-Barciab, Ana I. Ballesterosb, Javier Fragac, Ramon Colomerb, and Alfonsa Friera. Skeletal muscle and solitary bone metastases from malignant melanoma: multimodality imaging and oncological outcome. Melanoma Research 2018, 28:562–570

16. Mercer NS, Devaraj VS. Intramuscular metastatic melanoma with an unknown primary. Br J Plast Surg. 1990;43(3):367-368

17. Calvert J, Pigg TS. A case of melanotic sarcoma. Trans Pathol Soc Lond. 1898;49:297

18. Goforth JL. Malignant melanoma of the vulva. Surg Gynaecol Obstet. 1926;43:322

19. Portilla G, Cruz A, Juan N, et al. Isolated rectus abdominis metastasis from melanoma, an extremely rare case. Int J Surg Case Rep. 2016;26:121-123

20. Moss ALH, Rees MJW. Metastatic malignant melanoma in muscle. Br J Plast Surg. 1984;37:250

21. Herring CL, Harrelson JM, Scully SP. Metastatic carcinoma to skeletal muscle – a report of 15 patients. Clin Orthop. 1998;355:272-281

22. Jenkins RW, Fisher DE. Treatment of Advanced Melanoma in 2020 and Beyond. J Invest Dermatol. 2021;141(1):23-31

23. Tanda ET, VanniI,Boutros A, et al.Current State of Target Treatment in BRAF MutatedMelanoma. Front Mol Biosci. 2020;7:154

24. Hauschild A, Ascierto PA, Schadendorf D, Grob JJ, Ribas A, Kiecker F, Dutriaux C, Demidov LV, Lebbé C, Rutkowski P, Blank CU, Gutzmer R, Millward M, Kefford R, Haas T, D'Amelio A Jr, Gasal E, Mookerjee B, Chapman PB. Long-term outcomes in patients with BRAF V600-mutant metastatic melanoma receiving dabrafenib monotherapy: Analysis from phase 2 and 3 clinical trials. Eur J Cancer. 2020. 125: 114-120.

25. Robert C, Grob JJ, Stroyakovskiy D, Karaszewska B, Hauschild A, Levchenko E, Chiarion Sileni V, Schachter J, Garbe C, Bondarenko I, Gogas H, Mandalá M, Haanen JBAG, Lebbé C, Mackiewicz A, Rutkowski P, Nathan PD, Ribas A, Davies MA, Flaherty KT, Burgess P, Tan M, Gasal E, Voi M, Schadendorf D, Long GV. Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma. N Engl J Med. 2019. 381(7): 626-636.

JMRO

Journal of Medical and Radiation Oncology

Journal homepage: www.jmedradonc.org

The Medical Physicist and Cancer Care: Transcending Your Comfort Zone

Author: *Monica-Emilia Chirilă*

Affiliation: *MVision AI Oy, Helsinki, Finland*

Corresponding Author: Monica-Emilia Chirilă **e-mail**: monica.emilia.chirila@gmail.com

Professor M. Saiful Huq is an esteemed Medical Physicist, Past-President of the American Association of Physicists in Medicine (AAPM), Professor of Radiation Oncology at the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA and the Director of Medical Physics Division for the UPMC CancerCenter.

Dr. Huq is responsible for the development of scientific activities of a large group of physicists and management of clinical medical physics operations of 21 cancer centers in western Pennsylvania, USA. He has served as an expert on many International Atomic Energy Agency (IAEA) initiatives, developing various documents (example, author of IAEA TRS398 CoP, author of IAEA/AAPM CoP on small field dosimetry, Member of the IAEA research project "Testing the recommendations of the IAEA AAPM Code of Practice for the Dosimetry of Static Small Photon Fields") which provide guidance to the worldwide radiotherapy community regarding various aspects of cancer therapy using external beam radiation.

Interviews

1. Professor Huq, how would you describe your professional journey?

From childhood I was interested in physics. My challenge was to find ways to coalesce my interest in physics with one of the values that I grew up with – rendering public service. I wanted to undertake initiatives that would be most impactful for me in my life but most importantly do something that would have a lasting impact on other people's lives. As I was going through this soul-searching process I stumbled into Medical Physics and became a medical physicist. Early on in my career I discovered that the most satisfying days were those in which I was involved in the *team-based care* of patients – when I left work at night, legs aching, knowing that my team's effort bettered a patient's life. Most importantly, I sought to have a *sense of purpose* and impact on the lives of patients I took care of. I developed strong connections with my patients and shepherded them through challenging,

https://doi.org/10.53011/JMRO.2022.01.09
2784 – 0131/Copyright 2022 The Author(s).

emotional junctures in their lives. Some defining moments of my life were seeing a smile on the face of a mother on the last day of treatment of her young child who I helped treat with radiation and seeing a healthy newborn of a young breast cancer patient who was pregnant at the time of treatment and who wanted to keep the baby while getting radiation treatment of her breast. These events were very inspirational to me and continued to be so rewarding that I became fully immersed and enamored with my career as a medical physicist. I also sought to impact the field and make a difference on a greater scale as a clinical physicist, as an academic physicist via research initiatives, and by growing organized medical physics services. As a result, I got involved with many committees of the American Association of Physicists in Medicine (AAPM) and Task Group activities, other professional societies, and organizations such as IAEA, ASTRO and radiation oncology and medical physics societies around the world.

At the core of my enjoyment and passion in these initiatives was working in teams of motivated people with diverse backgrounds and ideas and a shared mission. Indeed, my life's most satisfying work has always involved succeeding as a team – in education, in clinical care, in research and otherwise. I am now drawn toward the team driving organized efforts to have AAPM, different professional societies, advocacy groups, governmental organizations, healthcare organizations, and other stakeholders lead the medical physics and radiation oncology profession into the future – in North America and beyond its borders.

2. Who influenced you and who were your role-models?

My parents. I was born in a middle-class family in Bangladesh. Making a difference in people's lives through public service was considered very important in our family. My father spent his entire professional life working for an organization that provided volunteer services to the country. My elder brother became a national role model for all age groups of people in the country, young and old, for his services as a business person and as the beloved mayor of the northern part of the capital city, Dhaka. One of my younger brothers dedicated his career to the service of the nation by working in the Bangladesh Army. The spirit of rendering public service was instilled in me very early in my life by my parents.

3. What are the qualities of a leader, in your opinion?

There are many qualities that a great leader must possess. One can write a book on it. I will mention just a few of them here. *Self-awareness* and *willingness to learn* are two very important qualities. Self-awareness means recognizing your strengths and weaknesses. You must know what you do not know and pretending that you know it all does not help. Practicing humility and learning sets up a great example for other leaders and followers. So, leaders should be great learners*. Humility* is one the most important qualities that a leader should have.

A good leader must be *visionary*, *thoughtful*, and know *how to inspire, motivate, and engage* his/her followers/team members over the long haul. It is important for a leader *to be a good listener* and *connect* with the team members, *build strong relationships* and mutual trust with them. Trust is the cornerstone of a good leader-follower relationship. A successful leader *thinks critically, establishes correct vision/goals/purpose*, and *develops a plan/process* to achieve them. A good plan should always include opportunities for growth of the team members. The leader must *communicate* the vision/purpose/goals and the plan to accomplish them to all team members effectively; *inspire* the team members so that they find meaning in achieving the goal. It is important to recognize the team members appropriately, their values, and their contributions. Establishment of such a positive environment leads to a sustainable relationship between the leader and the followers and success of the project.

4. What about a mentor? What makes someone a good mentor?

A good mentor is someone who enjoys the many rewards of giving back, understands the potential for growth of the mentee, cares for her/his mentee, and promotes professional and career

development of the mentee. They are committed to the success of the mentee. Great mentors instill *self-awareness, value, integrity, and empathy* in the mentee. They do so by building a strong trustworthy partnership and professional relationship with the mentee and sharing knowledge, expertise, and skills with them. Good mentors create structure around meeting times, sit down with the mentee and set goals, expectations, milestones, and demand accountability. They *make the mentees think for themselves instead of giving answers* and *provide constructive feedback and guidance*. Good mentors are positive by nature and always see a cup as half-full rather than half-empty which always leaves a positive influence on the mentee. It is important to recognize that great mentors learn as much from the mentee as the mentee learns from them.

Great mentors always enjoy seeing the amazing transition that their mentees undergo in their professional and personal career through this mentor/mentee relationship.

5. What are your projects for the future?

I am passionate about partnering with health care facilities and organizations globally especially in low-and middle-income countries to help improve the quality of care provided to cancer patients. As I mentioned earlier, I have been working with an NGO, „Dăruiește Viața", and their team to build a radiotherapy department in the children's hospital that they are building in Bucharest, Romania. I am involved with the local leadership in Bangladesh to help build the capacity of radiation oncology professionals (radiation oncologists, medical physicists, radiation therapists) through the establishment of structured hybrid education and training programs. Other exciting future projects include, but are not limited to, establishing a cooperative group clinical trial network in Africa. To support this initiative, I am working with a team of highly dedicated medical physicists and physicians from Africa and the United States to build a cloud-based comprehensive cancer center that will be powered by artificial intelligence technology to provide support for protocol development, data quality and data management, remote treatment planning and quality assurance activities, audit, site credentialing, remote peer-review, education and training and other activities that are necessary to provide a high-quality safe care to cancer patients treated with radiation therapy. Another important African initiative include working with the local leadership and other stakeholders to help establish accredited graduate medical educations programs in medical physics, clinical medical physics residency programs, and certification of clinically qualified medical physicists in Africa. I firmly believe that successful implementation of these programs will represent a paradigm shift in how cancer patients will be treated in Africa for decades to come.

6. What are in your opinion the good parts in working in radiation oncology field in the low-and-middle-income countries?

Published data show that cancer burden is expected to almost double over the next 20 years in low-and-middle income countries (LMICs). About 60-70% of the patients in the LMICs will receive radiation therapy as part of their treatment. Currently, about 80% of radiation treatments in LMICs are palliative. The majority of cases that the patients present with are at stage III or IV, making palliative radiotherapy and end-of-life care the only possible form of treatment. Most developing countries do not have the resources or infrastructure to prevent, diagnose, or treat this growing burden of cancer. The access to care is very limited in these LMIC's and the lack of access to cancer care has tremendous impact on patients and families. This dire situation in the LMICs presents an opportunity for us to get involved. Professionally we will be exposed to a different type of patient population in a very different cultural setting with an amazing opportunity for tremendous personal and professional growth and hence much personal and professional satisfaction. A small effort by each of us can make a huge difference in the lives of these patients and their families. Together, we can make a big difference to the well-being of the global patient population that we serve.

7. What advice would you give to a young medical physicist or radiation oncologist?

Decide early in your career what it is that you love to do – clinical work, research, or some combination of the two, or something else. Your profession should not be a "job". You should love what you do. Only then will you be able to make a true difference in the lives of the cancer patients that we serve. Our profession is a very rewarding profession. There are tremendous opportunities that lie ahead of you. Artificial intelligence is already in the space of radiation oncology. Flash radiotherapy using photon beams on a conventional linac platform will soon become a reality. In your career you will be dealing with these and other exciting new technologies. Using these and other new tools, you will be able to provide a quality of care to our patients that we may not have been able to provide to date. This is very exciting, and I believe will be a truly rewarding experience.

Collaborate. Collaboration will open a world of opportunities for you.

Volunteer. I ask you to give an hour or two of your time a week to learn about the needs of the healthcare considerations of the larger global community, especially the community of low-and-middle-income countries. Give a month of your professional career a year or every other year serving the patient population in the low-and-middle-income countries. This experience can be truly rewarding and enjoyable and a win-win for both you and the patient population around the world.

** Some excerpts of this interview were taken from an AAPM Newsletter Article: Vol 44, No 2, March-April, 2019*

JMRO

Journal of Medical and Radiation Oncology

Journal homepage: www.jmedradonc.org

The Journey of Learning and the Healing Power of Art – A Discussion with Dr. Berardino De Bari

Author: *Monica-Emilia Chirilă*

Affiliation: *MVision AI Oy, Helsinki, Finland*

Corresponding Author: Monica-Emilia Chirilă **e-mail**: monica.emilia.chirila@gmail.com

Dr. Berardino De Bari is an Italian Radiation Oncologist based in Switzerland, recognized as one of the European experts on prostate cancer. Apart from his clinical activity, he is also involved in educational activities of ESTRO, IAEA and ESO. He is also a musician - composer and singer.

How would you describe yourself in a few words to somebody who does not know you?

…You mean professionally?

Mainly yes, but not exclusively - if you think you can share personal thoughts, too, they are well received.

It's a difficult question… It has never been easy for me to speak about myself…

Then maybe you could tell us what your friends and colleagues say about you, so we get a mirrored image.

They say that I'm sincere and that the discussions with me could be hard. They often say that quite often my opinions are correct but diplomacy is not my strong point. Sometimes I do not find the best way to express my opinion, but I am working on it, especially since I became Chief of department. They also say that I know many people but I also like to have time to be alone, to have time for myself, for my passions, to take time to recover from the emotions associated to work. At the same time, they say that they could spent great time with me, as I have a lot of interests, and I like see people smiling and spending good moments with me. They say to appreciate this "social side" of me.

https://doi.org/10.53011/JMRO.2022.01.10

Published by Casa Cărții de Știință

I believe that honestly mentioning the things you are trying to improve can be important for other colleagues who are working on establishing themselves as respected professionals. The "myth" of having to be close to perfection (or at least creating this image) in order to be successful, can be discouraging.

In general, we can say that a day in which we do not learn something new is a lost day.

I graduated in 2004 at the Catholic University of Rome, and completed my Radiation Oncology residency in 2008. I learned a lot there from Professor Cellini, Professor Trodella, and Professor Valentini. Then I worked in Lyon, Brescia, Lausanne and Besançon. I changed a lot and this was not an advantage from an academic point of view, because it takes time to develop projects which are necessary for evolving scientifically. Nevertheless, I am senior lecturer of the University of Lausanne, , but I did not complete, at least not for now, my path to professorship. At the same time, the good part of changing place is that I could see different places, habits, meet different people, and become aware of good and bad aspects of our profession. Education never stops. We learn every day. We also make mistakes, but we learn from them and try to avoid those errors that might have an impact on patients. Error is a part of our personal and professional life, so who thinks to be or to became perfect is far from the truth and reality.

I am glad that you mentioned the importance of the education; because I know you are actively involved in the educational activities of the European Society for Radiation Oncology (ESTRO), International Atomic Energy Agency (IAEA) and European School of Oncology (ESO). I was wondering when did you start to get involved and what is your personal motivation to invest your time and energy in these activities, in addition to your clinical work? Teaching others and helping them grow represents an effort that cannot be neglected.

My first involvement in ESTRO activities was in 2009, when I started working on the FALCON project, an educational project aiming at improving contouring skills of participants to onsite and online workshops. Professor Valentini invited me to join this project, together with many other colleagues. First workshop took place in 2010 in London. Soon, I became an ESTRO Fellow and I participated in ESTRO Agora meeting and then I started to teaching in ESTRO courses – The Multidisciplinary Course on Prostate Cancer and the Evidence-Based Radiation Oncology Course. Then I started my collaboration with IAEA, which allowed me to meet people from many parts of the world, including Central Africa, Middle and Eastern Asia, and these meetings changed my perspective. We are sometimes unsatisfied about the 2-3 weeks waiting time for obtaining an MRI for our patients, but while interacting with colleagues from other countries I found out that some people have to deal with a waiting list of 6 months for starting radiotherapy! So, I realized I am part of the category which is very lucky, from the professional point of view, and the things that did not work perfectly in our departments became less important when compared to such a kind of very complicated situation in other parts of the world. It was a great opportunity to work with those people and I tried to share with these colleagues... not all that I know – but all the doubts that I have. I tried to make them understand that we must reinvent our job every day, because we have to treat patients with characteristics that were not included in the clinical trials. Also, I took this teaching activity as an opportunity to update my knowledge, because while preparing each lecture I am searching for information, new trials, new guidelines etc.... And so my colleagues and my patients benefit from this continuous personal upgrading, too.

More recently, I started a very fruitful collaboration with the European School of Oncology, and we created together some interesting pathways that are available for free in the ESO website and that are regularly updated. It's a much more web-based educational approach, and I learnt a lot also from this experience. We are working on a new exciting project for Radiation Oncologists…but I could not say more for the instance…

You also mentioned working in different clinics from different countries. I was wondering what differences you saw between the health systems of Italy, France and Switzerland. What are the best parts of each of them?

I consider myself lucky for having worked in big centers. In Lyon I started my activity as a specialist and I had a lot of responsibilities since the beginning of my activity, which was something that was challenging, but also helped me grow. Then in Brescia I faced other mentalities, other ways of doing things – not better, not worse, but simply different when compared to Rome and to Lyon. When you are young you have strong opinions, and so was I, it has been important to discuss with people who had motivated professional doubts, and made me aware that what I knew was not an "absolute" truth. In Lausanne I realized how important it is to have the financial and logistic support for the professional projects. Of course, we have to take in account that Switzerland is a small country – it is not the same to have 3000 patients or 900 patients per year – you have more time for them. And that it is a rich country. However, I discovered some constraints related to the health insurances - the reimbursement for the treatments that do not meet a certain level of evidence could be refused. From the social point of view, it is understandable, because the resources of the Health System have to be used efficiently. A serious external control is necessary. We just have to make sure that those who decide if the treatment has enough benefit to get reimbursed are neutral and do not have any conflict of interest, and I'm not sure that Insurances are really independent... At the same time, from a professional and human point of view, it is very difficult to have conversations with some patients who hope for a second line or third line expensive treatment which is denied by the insurance companies. In France and Italy this situation is very rare.

In Italy there are differences between regions – in the North the technology is more available. In 2013, when the Tomotherapy was considered the ultimate technological solution, there were 23 machines in the North, from Aosta to Rimini, and only 4 in the rest on the country, so the patients were coming from the South to be treated in the Northern centers. Tomotherapy is for sure a good machine, but technology is not the only thing that matters, it is a useful tool, but not "the solution". In France and Switzerland there are no such differences in the regions. However, I do not know if it would be possible to apply Swiss rules to Italian people. We are a quite creative, artistic population, usually reluctant in easily accepting some strict rules; and we find solutions where they do not seem to exist. An example can be seen when comparing the reactions on social media of Italian and Swiss people to Covid-19 restrictions - they were totally different.

You are considered a European expert on prostate cancer. What is your opinion on current controversies and further directions of research for this type of malignancy?

Personally, I have three points of interest. First - the combination of the new molecules with radiotherapy. The androgen deprivation therapy is used in high-risk patients and in metastatic cases, but it would be interesting to see what would be the outcomes if Enzalutamide, Apalutamide, Abiraterone or Cabazitaxel would be used earlier in the evolution of a case and integrated with radiotherapy. Of course, like in breast cancer, seeing the results of an intervention takes time, because of the natural history of the disease.

Second - I think it would be important to understand the role of newer imaging methods, like PSMA, in deciding on the treatment volumes and, finally their impact on the clinical results of the patients. The current recommendations are usually based on clinical trials in which the patients were evaluated with investigations which were not so accurate (CT scan, bone scintigraphy), so we do not know for sure which was the real extent of the disease that was treated. And, finally, if the results of these trials could be applied to the modern populations of patients, staged with modern imaging techniques.

And the third thing would be the further investigation of the role of immunotherapy in prostate cancer. I could not forget that one of the first randomized trials on immunotherapy with radiotherapy was on prostate cancer, and it was considered negative because of a p value of 0.052, if I'm not wrong… I think that there is something to explore better in this field…

Finally, I would want to touch a topic which you briefly mentioned before, when saying that Italians have an artistic, creative side. What is your opinion on mixing science and art? Do you have any art-related activities?

I must say that I am biased, because I was trained in Professor's Valentini center in Rome, where the concept of ART is developed, in both ways: Advanced Radiation Therapy and also integration of different forms of Art in patients' therapeutic journey. The bunkers where the linear accelerators are installed are decorated with images reproducing ancient Roman buildings, so the patients can find themselves surrounded by familiar, esthetic images. Recently, in Copenhagen, at ESTRO, a new project of this team was presented, allowing the patients to listen to favorite songs or watch video clips during their treatments using some portable devices. It has been shown that art could have has a positive impact on the clinical outcomes of the patients. However, when you want to implement the same thing in another environment you must face challenges - either the opposition of "non-believer" colleagues, either official requirement for approval of hospital use, where there are clear specifications, like, for example, all the walls should be white, all the doors should be green and all the floors should be blue.

We are replacing the machines here, where I work, and I already discussed with our colleagues that we should not leave the walls plain white - maybe contacting the art schools which are close to our center and organize some display of their works of art within our department - the waiting area the bunker... My colleagues start to understand, too, that it can make a difference for the people that spend a lot of time within those walls during the radiation treatment.

I also noticed that the colleagues who have some artistic side or simply appreciating a form of art, it does not matter which one, have a different approach when communicating with patients, and the patients are noticing this. If you like to sing, for example, it does not mean that you are not serious and professional. For example, I like to write songs, to compose music. I have displayed in my office two posters of renowned French singers. Sometimes, when patients are coming, the dialogue starts around this topic and people suddenly become more open and comfortable. Of course we get to the medical reason of their visit, and we have a professional conversation, but they appreciate that we can have a discussion on another topic than their disease. I see no special reason for separating these two worlds.

Indeed, while facing the challenge of the disease, the fight might become a little easier if we focus on the beautiful sides of the life, pictured by the artists. Fortunately, it seems to have a positive, "healing", effect on both patients and caregivers, which share a part of the same burden.

Thank you for kindly accepting to share your thoughts with us.


accord

După tratamentul cu sorafenib, STIVARGA® (regorafenib) a demonstrat o supraviețuire extinsă, în cazul pacienților cu Carcinom Hepatocelular nerezecabil (CHCn)[1]

Sorafenib: opțiune de tratament de primă linie ca TKI cu beneficii dovedite în privința OS

STIVARGA®: beneficiu de supraviețuire dovedit după evoluția bolii în timpul tratamentului cu sorafenib[2]

Rezultate în SHARP

OS ÎMBUNĂTĂȚIT CU

31%

la pacienți cu CHC nerezecabil[3]

Rezultate în RESORCE

OS ÎMBUNĂTĂȚIT CU

37%

la pacienți a căror boală a evoluat în timpul tratamentului cu sorafenib[1]

Analiza exploratorie demonstrează

UN OS MEDIAN DE

26 LUNI

la pacienți tratați cu secvența sorafenib - STIVARGA®[4]

Rezultatele analizei exploratorii retrospective, bazată pe studiul pivot de fază 3 RESORCE, sugerează că pacienții cu CHC avansat, tratați cu sorafenib urmat de STIVARGA®, au avut un timp median de la începerea tratamentului cu sorafenib până la deces de 26,0 luni (95% CI, 22,6-28,1), comparativ cu 19,2 luni (95% CI, 1 ,3-22,8) pentru cei tratați cu sorafenib urmat de placebo.

Rezultatele de îmbunătățire a supraviețuirii confirmă secvența sorafenib - STIVARGA® ca o opțiune dovedită de tratament, în peisajul terapeutic actual al CHCn[1,2,4]

Referințe:
1. J. Bruix et al, The Lancet, Vol 389, Jan. 2017.
2. Rezumatul Caracteristicilor Produsului Stivarga - aug. 2021.
3. JM Llovet et al, N Engl. J Med.,2008;359(4),378-390.
4. RS Finn et al, J Hepatol. 2018;69(2):353-358.

Pentru informații suplimentare consultați Rezumatul Caracteristicilor Produsului Stivarga® (regorafenib) disponibil pe website-ul Agenției Europene a Medicamentului: https://www.ema.europa.eu

Pentru întrebări medicale despre acest medicament vă rugăm să ne contactați la adresa: medical-info-ro@bayer.com

Acest material promoțional este destinat profesioniștilor din domeniul sănătății. Profesioniștii din domeniul sănătății sunt încurajați să raporteze evenimentele adverse apărute la pacienții care utilizează Stivarga® (regorafenib), către Agenția Națională a Medicamentului și a Dispozitivelor Medicale din România: Fax: +4 0213 163 497; e-mail: adr@anm.ro; https://adr.anm.ro/ sau către reprezentanța locală a deținătorului autorizației de punere pe piață: Bayer SRL, Tel: + 40 21 528 59 09; Fax: +4 0215 285 938; e-mail: pharmacovigilance_romania@bayer.com

SC Bayer SRL
Șos. București – Ploiești nr. 1A, clădire B, etaj 1,
Sector 1, 013681,
București, România

PP-STI-RO-0010-1

OPDIVO (nivolumab) - Informaţii esenţiale din rezumatul caracteristicilor produsului

Consultaţi Rezumatul Caracteristicilor Produsului (RCP) înainte de prescriere. Compoziţia calitativă şi cantitativă: Fiecare ml de concentrat pentru soluţie perfuzabilă conţine nivolumab 10 mg. Indicaţii terapeutice: Melanom: OPDIVO este indicat în monoterapie sau în asociere cu ipilimumab pentru tratamentul melanomului în stadiu avansat (nerezecabil sau metastazat) la adulţi. În comparaţie cu monoterapia cu nivolumab, o creştere a supravieţuirii fără progresia bolii (SFP) şi a supravieţuirii generale (SG) pentru asocierea nivolumab cu ipilimumab este stabilită numai la pacienţii cu expresie tumorală redusă a PD-L1 (vezi pct. 4.4 şi 5.1 din RCP). Tratament adjuvant al melanomului: OPDIVO în monoterapie este indicat pentru tratamentul adjuvant al melanomului extins la ganglionii limfatici sau metastazat, la adulţii la care s-a efectuat rezecţie completă (vezi pct. 5.1 din RCP). Cancer bronho-pulmonar altul decât cel cu celule mici (NSCLC): OPDIVO în asociere cu ipilimumab şi 2 cicluri de chimioterapie pe bază de săruri de platină este indicat pentru tratamentul de primă linie al cancerului bronho-pulmonar altul decât cel cu celule mici metastazat, la adulţii ale căror tumori nu prezintă mutaţie sensibilizantă EGFR sau translocaţie ALK. OPDIVO în monoterapie este indicat pentru tratamentul cancerului bronho-pulmonar altul decât cel cu celule mici local avansat sau metastazat, după tratamentul anterior cu chimioterapie, la adulţi. Mezoteliom pleural malign (MPM): OPDIVO în asociere cu ipilimumab este indicat pentru tratamentul de primă linie al mezoteliomului pleural malign nerezecabil, la adulţi. Carcinom renal (RCC): OPDIVO este indicat ca monoterapie pentru tratamentul carcinomului renal avansat după terapie anterioară, la adulţi. OPDIVO în asociere cu ipilimumab este indicat pentru tratamentul de primă linie al carcinomului renal avansat cu prognostic intermediar/nefavorabil, la adulţi (vezi pct. 5.1 din RCP). OPDIVO în asociere cu cabozantinib este indicat pentru tratamentul de primă linie al carcinomului renal avansat, la adulţi (vezi pct. 5.1 din RCP). Limfom Hodgkin clasic (LH clasic): OPDIVO în monoterapie este indicat pentru tratamentul limfomului Hodgkin clasic recidivat sau refractar după transplant autolog de celule stem (TACS) şi tratament cu brentuximab vedotin la adulţi. Cancer scuamos de cap şi gât (SCCHN): OPDIVO în monoterapie este indicat pentru tratamentul cancerului scuamos de cap şi gât recurent sau metastazat, la adulţi la care boala progresează în timpul sau după terapie pe bază de săruri de platină (vezi pct. 5.1 din RCP). Carcinom urotelial: OPDIVO în monoterapie este indicat pentru tratamentul carcinomului urotelial nerezecabil local avansat sau metastazat, la adulţi, după eşecul terapiei anterioare pe bază de săruri de platină. Cancer colorectal (CRC) cu deficienţă de reparare a nepotrivirii ADN-ului (dMMR) sau cu instabilitate microsatelită de grad înalt (MSI-H): OPDIVO în asociere cu ipilimumab este indicat pentru tratamentul cancerului colorectal metastazat cu deficienţă de reparare a nepotrivirii ADN-ului sau cu instabilitate microsatelită de grad înalt, după chimioterapie anterioară pe bază de asocieri de fluoropirimidină, la adulţi (vezi pct. 5.1 din RCP). Carcinom scuamos esofagian (OSCC): OPDIVO în monoterapie este indicat pentru tratamentul carcinomului scuamos esofagian avansat, nerezecabil, recurent sau metastazat, după chimioterapie anterioară pe bază de fluoropirimidine în asociere cu săruri de platină, la adulţi. Tratament adjuvant al cancerului esofagian sau de joncţiune eso-gastrică (OC sau GEJC): OPDIVO în monoterapie este indicat pentru tratamentul adjuvant al cancerului esofagian sau de joncţiune eso-gastrică, la pacienţii adulţi care prezintă boală patologică reziduală după tratament neoadjuvant anterior cu chimioradioterapie (vezi pct. 5.1 din RCP). Adenocarcinom gastric, de joncţiune eso-gastrică (GEJ) sau esofagian: OPDIVO în asociere cu chimioterapie combinată pe bază de fluoropirimidine şi săruri de platină este indicat pentru tratamentul de primă linie al adenocarcinomului gastric, de joncţiune eso-gastrică sau esofagian, avansat sau metastazat, HER2-negativ, la pacienţii adulţi ale căror tumori prezintă expresie PD-L1 cu un scor combinat pozitiv (CPS) ≥ 5. Doze şi mod de administrare: Testare PD-L1: Dacă este specificat în indicaţie, selectarea pacientului pentru tratamentul cu OPDIVO pe baza expresiei tumorale a PD-L1 trebuie confirmată printr-un test validat (vezi pct. 4.1, 4.4 şi 5.1 din RCP). Doze: *OPDIVO în monoterapie:* Doza recomandată de OPDIVO este fie de 240 mg nivolumab la fiecare 2 săptămâni, sau 480 mg la fiecare 4 săptămâni (vezi pct. 5.1 din RCP), în funcţie de indicaţie, după cum urmează: *Melanom (în stadiu avansat sau pentru tratament adjuvant) şi, respectiv, Carcinom renal:* 240 mg la fiecare 2 săptămâni, pe durată a 30 minute sau 480 mg la fiecare 4 săptămâni, pe durata a 60 minute; *Cancer esofagian sau de joncţiune eso-gastrică (tratament adjuvant):* 240 mg la fiecare 2 săptămâni, pe durata a 30 minute sau 480 mg la fiecare 4 săptămâni, pe durata a 30 minute, pentru primele 16 săptămâni, urmat de 480 mg la fiecare 4 săptămâni, pe durata a 30 minute; *Cancer bronho-pulmonar altul decât cel cu celule mici, Limfom Hodgkin clasic, Cancer scuamos de cap şi gât, Carcinom urotelial şi, respectiv, Carcinom scuamos esofagian:* 240 mg la fiecare 2 săptămâni, pe durata a 30 minute. *OPDIVO în asociere cu ipilimumab: Melanom:* Doza recomandată este de nivolumab 1 mg/kg în asociere cu ipilimumab 3 mg/kg, administrată intravenos la fiecare 3 săptămâni pentru primele 4 doze. Această este urmată apoi de o a doua fază în care nivolumab este administrat în monoterapie pe cale intravenoasă fie în doză de 240 mg la fiecare 2 săptămâni sau în doză de 480 mg la fiecare 4 săptămâni. În faza de monoterapie, prima doză de nivolumab trebuie administrată: la interval de 3 săptămâni după ultima doză din terapia asociată nivolumab cu ipilimumab, dacă se utilizează doza de 240 mg la fiecare 2 săptămâni; sau la interval de 6 săptămâni după ultima doză din terapia asociată nivolumab cu ipilimumab, dacă se utilizează doza de 480 mg la fiecare 4 săptămâni (vezi, de asemenea, Tabelul 2 din RCP pentru duratele perfuziei); *Mezoteliom pleural malign:* Doza recomandată este de 360 mg nivolumab administrat intravenos pe durata a 30 minute la fiecare 3 săptămâni în asociere cu 1 mg/kg ipilimumab administrat intravenos pe durata a 30 minute la fiecare 6 săptămâni. Tratamentul se continuă până la 24 luni la pacienţii fără progresia bolii; *Carcinom renal şi cancer colorectal dMMR sau MSI-H:* Doza recomandată este de nivolumab 3 mg/kg în asociere cu ipilimumab 1 mg/kg, administrată intravenos la fiecare 3 săptămâni pentru primele 4 doze. Aceasta este urmată apoi de o a doua fază în care nivolumab este administrat în monoterapie pe cale intravenoasă fie în doză de 240 mg la fiecare 2 săptămâni sau în doză de 480 mg la fiecare 4 săptămâni (numai pentru RCC). În faza de monoterapie, prima doză de nivolumab trebuie administrată: la interval de 3 săptămâni după ultima doză din terapia asociată nivolumab cu ipilimumab, dacă se utilizează doza de 240 mg la fiecare 2 săptămâni; sau la interval de 6 săptămâni după ultima doză din terapia asociată nivolumab cu ipilimumab, dacă se utilizează doza de 480 mg la fiecare 4 săptămâni (numai pentru RCC) (vezi, de asemenea, Tabelul 3 din RCP pentru duratele perfuziei). *OPDIVO în asociere cu cabozantinib: Carcinom renal:* Doza recomandată este fie nivolumab 240 mg la fiecare 2 săptămâni sau nivolumab 480 mg la fiecare 4 săptămâni, administrat pe cale intravenoasă, în asociere cu cabozantinib 40 mg în fiecare zi, administrat pe cale orală (vezi, de asemenea, Tabelul 4 din RCP pentru duratele perfuziei). *OPDIVO în asociere cu ipilimumab şi chimioterapie: Cancer bronho-pulmonar altul decât cel cu celule mici:* Doza recomandată este de 360 mg nivolumab administrat intravenos pe durata a 30 minute la fiecare 3 săptămâni în asociere cu 1 mg/kg ipilimumab administrat intravenos pe durata a 30 minute la fiecare 6 săptămâni şi chimioterapie pe bază de săruri de platină administrată la fiecare 3 săptămâni. După finalizarea a 2 cicluri de chimioterapie, tratamentul se continuă cu 360 mg nivolumab administrat intravenos la fiecare 3 săptămâni în asociere cu 1 mg/kg ipilimumab la fiecare 6 săptămâni. Tratamentul este recomandat până la progresia bolii, toxicitate inacceptabilă sau până la 24 luni la pacienţii fără progresia bolii. *OPDIVO în asociere cu chimioterapie: Adenocarcinom gastric, de joncţiune eso-gastrică sau esofagian*: Doza recomandată este de 360 mg nivolumab, administrată intravenos pe durata a 30 minute în asociere cu chimioterapie pe bază de fluoropirimidine şi săruri de platină administrată la fiecare 3 săptămâni sau de 240 mg nivolumab administrat intravenos pe durata a 30 minute în asociere cu chimioterapie pe bază de fluoropirimidine şi săruri de platină administrată la fiecare 2 săptămâni (vezi pct. 5.1 din RCP). Tratamentul cu nivolumab este recomandat până la progresia bolii, toxicitate inacceptabilă sau până la 24 luni la pacienţii fără progresia bolii. *Durata tratamentului:* Tratamentul cu OPDIVO, fie sub formă de monoterapie sau în asociere cu ipilimumab, trebuie continuat atât timp cât se observă beneficii clinice sau până când nu mai este tolerat de pacient (şi până la durata maximă a terapiei, dacă este specificată pentru o indicaţie). În terapia adjuvantă, durata maximă a tratamentului cu OPDIVO este de 12 luni. În cazul administrării de OPDIVO în asociere cu cabozantinib, tratamentul cu OPDIVO trebuie continuat până la progresia bolii, toxicitate inacceptabilă sau până la 24 luni la pacienţii fără progresia bolii. Tratamentul cu cabozantinib trebuie continuat până la progresia bolii sau toxicitate inacceptabilă. Consultaţi RCP-ul pentru cabozantinib. S-au observat răspunsuri atipice (şi anume, o creştere tranzitorie iniţială a dimensiunii tumorii sau leziuni mici noi apărute în primele câteva luni, urmate de reducerea dimensiunilor tumorilor). La pacienţii cu o stare clinică stabilă, care prezintă semne iniţiale de progresie a bolii, se recomandă continuarea tratamentului cu nivolumab sau cu nivolumab în asociere cu ipilimumab, până la confirmarea progresiei bolii. Nu se recomandă creşterea sau scăderea dozelor pentru OPDIVO administrat în monoterapie sau în asociere cu alţi agenţi terapeutici. Poate fi necesară amânarea sau oprirea administrării tratamentului în funcţie de profilul individual de siguranţă şi tolerabilitate. Recomandările privind oprirea definitivă sau întreruperea temporară a dozelor sunt prezentate în Tabelul 5 din RCP. Recomandările detaliate privind conduita terapeutică în cazul reacţiilor adverse mediate imun sunt prezentate la pct. 4.4 din RCP. Atunci când nivolumab este administrat în asociere cu alţi agenţi terapeutici, se va consulta RCP-ul acestor alţi agenţi terapeutici administraţi în asociere pentru informaţii privind dozele. Tratamentul cu OPDIVO în monoterapie sau în asociere cu alţi agenţi terapeutici trebuie oprit definitiv în caz de: reacţii adverse de grad 4 sau reacţii adverse recurente de grad 3; reacţii adverse de grad 2 sau 3 persistente în pofida abordării terapeutice. Pacienţilor trataţi cu OPDIVO trebuie să li se înmâneze Cardul de atenţionare pentru pacient şi să li se aducă la cunoştinţă riscurile administrării OPDIVO (vezi, de asemenea, prospectul). Atunci când OPDIVO este administrat în asociere cu ipilimumab, dacă se întrerupe temporar administrarea oricăruia dintre aceste medicamente, se va întrerupe temporar şi administrarea celuilalt medicament. Dacă se reia utilizarea după o amânare a administrării dozei, se poate relua administrarea fie a tratamentului asociat sau a OPDIVO în monoterapie, pe baza evaluării individuale a pacientului. Atunci când OPDIVO este administrat în asociere cu chimioterapie, se va consulta RCP-ul pentru celelalte medicamente incluse în terapia asociată pentru informaţii privind dozele. Nu se recomandă creşterea sau scăderea dozelor pentru OPDIVO. Dacă se întrerupe temporar administrarea oricăruia dintre medicamente, se poate continua administrarea celorlalte medicamente. Dacă se reia utilizarea după o amânare a administrării dozei, se poate relua administrarea fie a tratamentului asociat, a OPDIVO în monoterapie sau a tratamentului numai cu chimioterapie, pe baza evaluării individuale a pacientului. Atunci când OPDIVO este utilizat în asociere cu cabozantinib, modificările tratamentului prezentate în Tabelul 5 din RCP se aplică, de asemenea, şi pentru OPDIVO ca parte a tratamentului. În plus, în cazul creşterii valorilor serice ale enzimelor hepatice, la pacienţii cu RCC cărora li se administrează OPDIVO în asociere cu cabozantinib, se impun modificările tratamentului prezentate la pct. 4.2, secţiunea „*OPDIVO în asociere cu cabozantinib pentru tratamentul RCC*", din RCP. *Copii şi adolescenţi:* Siguranţa şi eficacitatea OPDIVO la copii cu vârsta sub 18 ani nu au fost încă stabilite. Datele disponibile în prezent pentru OPDIVO administrat în monoterapie sau în asociere cu ipilimumab sunt prezentate la pct. 4.8 şi 5.1 din RCP, dar nu se poate face nicio recomandare privind dozele. *Vârstnici:* Nu este necesară ajustarea dozei la pacienţii vârstnici (≥ 65 ani). Mod de administrare: OPDIVO este numai pentru administrare intravenoasă. OPDIVO nu trebuie administrat intravenos rapid sau în bolus. Când se administrează în asociere cu ipilimumab şi/sau chimioterapie, OPDIVO trebuie administrat primul urmat de administrarea ipilimumab (dacă este cazul) şi apoi de chimioterapie în aceeaşi zi. Pentru fiecare perfuzie se vor utiliza pungi şi filtre pentru perfuzie diferite. Pentru instrucţiuni privind pregătirea şi manipularea medicamentului înainte de administrare, vezi pct. 6.6 din RCP. Contraindicaţii: Hipersensibilitate la substanţa activă sau la oricare dintre excipienţii enumeraţi la pct. 6.1 din RCP. Atenţionări şi precauţii speciale pentru

utilizare: Trasabilitate: Pentru a avea sub control trasabilitatea medicamentelor biologice, numele și numărul lotului medicamentului administrat trebuie înregistrate cu atenție. Reacții adverse mediate imun: Atunci când nivolumab este administrat în asociere, se va consulta RCP-ul pentru celelalte medicamente incluse în terapia asociată înainte de inițierea tratamentului. Reacțiile adverse mediate imun au survenit cu o frecvență mai mare atunci când nivolumab a fost administrat în asociere cu ipilimumab, comparativ cu utilizarea nivolumab în monoterapie. Reacțiile adverse mediate imun au survenit cu o frecvență similară atunci când OPDIVO a fost administrat în asociere cu cabozantinib, comparativ cu utilizarea nivolumab în monoterapie. Prin urmare, recomandările privind reacțiile adverse mediate imun prezentate la pct. 4.4 din RCP sunt aplicabile pentru OPDIVO ca parte a tratamentului în asociere, cu excepția cazurilor în care se menționează specific. Majoritatea reacțiilor adverse mediate imun s-au ameliorat sau au ajuns la rezoluție prin conduită terapeutică adecvată, inclusiv inițierea corticoterapiei și modificarea tratamentului (vezi pct. 4.2 din RCP). Reacțiile adverse mediate imun care afectează mai mult de un aparat sau sistem pot să apară simultan. În cazul terapiei asociate s-au raportat, de asemenea, reacții adverse cardiace și pulmonare, inclusiv embolie pulmonară. Pacienții trebuie monitorizați continuu pentru depistarea reacțiilor adverse cardiace și pulmonare, dar și a semnelor clinice, simptomelor și rezultatelor anormale ale testelor de laborator sugestive pentru dezechilibre electrolitice și deshidratare înainte de inițierea tratamentului și periodic pe durata acestuia. Pacienții trebuie monitorizați continuu (timp de cel puțin 5 luni după administrarea ultimei doze) deoarece o reacție adversă la tratamentul cu nivolumab sau cu nivolumab în asociere cu ipilimumab poate apărea în orice moment în timpul sau după oprirea terapiei. Pentru mai multe informații privind atenționările și precauțiile speciale pentru utilizare, vezi pct. 4.4 din RCP. Interacțiuni cu alte medicamente și alte forme de interacțiune: Nivolumab este un anticorp monoclonal uman, astfel încât nu s-au efectuat studii privind interacțiunile farmacocinetice. Nu se anticipează ca efectul inhibitor sau inductor asupra enzimelor citocromului P450, al medicamentelor administrate concomitent, să influențeze profilul farmacocinetic al nivolumab. *Terapie imunosupresoare sistemică:* Trebuie evitată utilizarea corticosteroizilor sistemici și a altor terapii imunosupresoare la momentul inițial, înaintea inițierii tratamentului cu nivolumab, din cauza posibilei interferențe cu activitatea farmacodinamică. Cu toate acestea, corticoterapia sistemică și alte terapii imunosupresoare pot fi utilizate după inițierea administrării nivolumab în scopul tratării reacțiilor adverse mediate imun. Fertilitatea, sarcina și alăptarea: Sarcina: Nu există date din utilizarea nivolumab la femeile gravide. Alăptarea: Nu se cunoaște dacă nivolumab se excretă în laptele uman. Fertilitatea: Nu s-au efectuat studii privind efectul nivolumab asupra fertilității. Efecte asupra capacității de a conduce vehicule și de a folosi utilaje: Pacienților trebuie să li se recomande precauție atunci când conduc vehicule sau folosesc utilaje până în momentul în care au certitudinea că tratamentul cu nivolumab nu îi afectează negativ. Reacții adverse: Nivolumab în monoterapie: *Rezumatul profilului de siguranță:* În setul de date cumulat provenit din administrarea nivolumab în monoterapie pentru multiple tipuri de tumori (n = 3771), perioada minimă de monitorizare variind între 2,3 și 28 luni, cele mai frecvente reacții adverse (≥ 10%) au fost fatigabilitatea (46%), durerea musculo-scheletică (31%), diareea (26%), greața (24%), tusea (24%), erupțiile cutanate tranzitorii (24%), dispneea (18%), pruritul (18%), scăderea apetitului alimentar (18%), constipația (17%), durerea abdominală (16%), infecțiile tractului respirator superior (16%), artralgia (15%), febra (14%), vărsăturile (14%), cefaleea (13%) și edemul (11%). Majoritatea reacțiilor adverse au fost ușoare până la moderate (grad 1 sau 2). Pentru o perioadă de monitorizare de minim 63 luni în NSCLC, nu au fost identificate noi semnale de siguranță. Nivolumab în asociere cu ipilimumab: *Rezumatul profilului de siguranță:* Atunci când nivolumab este administrat în asociere cu ipilimumab, se va consulta RCP-ul pentru ipilimumab înainte de inițierea tratamentului. Pentru informații suplimentare privind profilul de siguranță al ipilimumab în monoterapie, vă rugăm consultați RCP-ul pentru ipilimumab. *Melanom:* În setul de date cumulat provenit din administrarea nivolumab 1 mg/kg în asociere cu ipilimumab 3 mg/kg la pacienți cu melanom (n = 448), perioada minimă de monitorizare variind între 6 și 28 luni, cele mai frecvente reacții adverse (≥ 10%) au fost erupțiile cutanate tranzitorii (52%), fatigabilitatea (46%), diareea (43%), pruritul (36%), greața (26%), febra (19%), scăderea apetitului alimentar (16%), hipotiroidismul (16%), colita (15%), vărsăturile (14%), artralgia (13%), durerea abdominală (13%), cefaleea (11%) și dispneea (10%). Majoritatea reacțiilor adverse au fost ușoare până la moderate (grad 1 sau 2). *RCC și CRC dMMR sau MSI-H:* În setul de date cumulat provenit din administrarea nivolumab 3 mg/kg în asociere cu ipilimumab 1 mg/kg pentru multiple tipuri de tumori (n = 666), perioada minimă de monitorizare variind între 17,5 și 27,6 luni, cele mai frecvente reacții adverse (≥ 10%) au fost fatigabilitatea (58%), diareea (41%), durerea musculo-scheletică (39%), erupțiile cutanate tranzitorii (38%), pruritul (35%), greața (30%), tusea (29%), febra (29%), durerea abdominală (22%), artralgia (22%), scăderea apetitului alimentar (22%), infecțiile tractului respirator superior (21%), vărsăturile (21%), cefaleea (19%), dispneea (19%), hipotiroidismul (18%), constipația (18%), edemul (inclusiv edemul periferic) (16%), ametelile (14%), hipertiroidismul (12%), xerodermia (11%), hipertensiunea arterială (10%). Majoritatea reacțiilor adverse au fost ușoare până la moderate (grad 1 sau 2); *MPM:* În setul de date provenit din administrarea nivolumab 3 mg/kg în asociere cu ipilimumab 1 mg/kg la pacienți cu MPM (n = 300), perioada minimă de monitorizare fiind de 22,1 luni, cele mai frecvente reacții adverse (≥ 10%) au fost fatigabilitatea (43%), diareea (31%), erupțiile cutanate tranzitorii (30%), durerea musculo-scheletică (27%), greața (24%), scăderea apetitului alimentar (24%), pruritul (21%), constipația (19%) și hipotiroidismul (13%). Majoritatea reacțiilor adverse au fost ușoare până la moderate (grad 1 sau 2). Nivolumab în asociere cu alți agenți terapeutici: *Rezumatul profilului de siguranță:* Atunci când nivolumab este administrat în asociere, înainte de inițierea tratamentului se va consulta RCP-ul pentru componentele respective ale terapiei asociate. În setul de date provenit din administrarea nivolumab 240 mg la fiecare 2 săptămâni sau 360 mg la fiecare 3 săptămâni în asociere cu chimioterapie la pacienți cu adenocarcinom gastric, de GEJ sau esofagian (n = 782), perioada minimă de monitorizare fiind de 12,1 luni, cele mai frecvente reacții adverse au fost neuropatia periferică (53%), greața (48%), fatigabilitatea (44%), diareea (39%), vărsăturile (31%), scăderea apetitului alimentar (29%), durerea abdominală (27%), constipația (25%), durerea musculo-scheletică (20%), febra (19%), erupțiile cutanate tranzitorii (18%), stomatita (17%), sindromul de eritrodisestezie palmo-plantară (13%), tusea (13%), edemul (inclusiv edemul periferic) (12%), cefaleea (11%) și infecțiile tractului respirator superior (10%). Incidențele reacțiilor adverse de grad 3-5 au fost de 76% pentru nivolumab în asociere cu chimioterapie și de 64% pentru tratamentul numai cu chimioterapie. Durata mediană a terapiei a fost de 6,75 luni (IÎ 95%: 6,11, 7,36) pentru nivolumab în asociere cu chimioterapie și de 4,86 luni (IÎ 95%: 4,47, 5,29) pentru chimioterapie. În setul de date provenit din administrarea nivolumab 360 mg la fiecare 3 săptămâni în asociere cu ipilimumab 1 mg/kg la fiecare 6 săptămâni și 2 cicluri de chimioterapie în NSCLC (n = 358), perioada minimă de monitorizare fiind de 6,5 luni, cele mai frecvente reacții adverse au fost fatigabilitatea (36%), greața (26%), erupțiile cutanate tranzitorii (25%), diareea (20%), pruritul (18%), scăderea apetitului alimentar (16%), hipotiroidismul (15%) și vărsăturile (13%). Majoritatea reacțiilor adverse au fost ușoare până la moderate (grad 1 sau 2). Durata mediană a terapiei a fost de 6,1 luni (IÎ 95% 4,93, 7,06) pentru nivolumab în asociere cu ipilimumab și chimioterapie și de 2,4 luni (IÎ 95% 2,30, 2,83) pentru chimioterapie. Nivolumab în asociere cu cabozantinib: *Rezumatul profilului de siguranță:* Atunci când nivolumab este administrat în asociere cu cabozantinib, se va consulta RCP-ul pentru cabozantinib înainte de inițierea tratamentului. Pentru informații suplimentare privind profilul de siguranță al cabozantinib în monoterapie, vă rugăm consultați RCP-ul pentru cabozantinib. *RCC:* În setul de date provenit din administrarea nivolumab 240 mg la fiecare 2 săptămâni în asociere cu cabozantinib 40 mg o dată pe zi la pacienți cu RCC (n =320), perioada minimă de monitorizare fiind de 16,0 luni, cele mai frecvente reacții adverse (≥ 10%) au fost diareea (64,7%), fatigabilitatea (51,3%), sindromul de eritrodisestezie palmo-plantară (40,0%), stomatita (38,8%), durerea musculo-scheletică (37,5%), hipertensiunea arterială (37,2%), erupțiile cutanate tranzitorii (36,3%), hipotiroidismul (35,6%), scăderea apetitului alimentar (30,3%), greața (28,8%), durerea abdominală (25,0%), disgeuzia (23,8%), infecțiile tractului respirator superior (20,6%), tusea (20,6%), pruritul (20,6%), artralgia (19,4%), vărsăturile (18,4%), disfonia (17,8%), cefaleea (16,3%), dispepsia (15,9%), ametelile (14,1%), constipația (14,1%), febra (14,1%), edemul (13,4%), spasmul muscular (12,2%), dispneea (11,6%), proteinuria (10,9%) și hipertiroidismul (10,0%). Majoritatea reacțiilor adverse au fost ușoare până la moderate (grad 1 sau 2). Pentru informații complete privind reacțiile adverse, vezi pct. 4.8 din RCP. Raportarea reacțiilor adverse suspectate: Profesioniștii din domeniul sănătății sunt rugați să raporteze orice reacție adversă suspectată la: Agenția Națională a Medicamentului și a Dispozitivelor Medicale din România, Str. Aviator Sănătescu nr. 48, sector 1, București 011478- RO, Tel: + 4 0757 117 259, Fax: +4 0213 163 497, e-mail: adr@anm.ro. Supradozaj: În studiile clinice, nu au fost raportate cazuri de supradozaj. Lista excipienților: Vezi pct. 6.1 din RCP. Incompatibilități: OPDIVO nu trebuie perfuzat concomitent în aceeași linie intravenoasă cu alte medicamente. Perioada de valabilitate: Flacon nedeschis: 3 ani. După pregătirea soluției perfuzabile: Stabilitatea fizico-chimică în timpul utilizării este dependentă de modalitatea de pregătire a soluției perfuzabile și de condițiile de păstrare (vezi pct. 6.3 din RCP). Din punct de vedere microbiologic, soluția perfuzabilă pregătită, indiferent de solvent, trebuie administrată imediat. Dacă nu poate fi administrată imediat, intervalele de timp și condițiile de păstrare în timpul utilizării, înainte de administrare, sunt responsabilitatea utilizatorului și, în mod normal, nu sunt mai mari de 7 zile la 2°C până la 8°C sau de 8 ore (din totalul de 7 zile de păstrare) la temperatura camerei (≤ 25°C). Este necesară respectarea tehnicilor de asepsie în timpul pregătirii soluției perfuzabile (vezi pct. 6.6 din RCP). Precauții speciale pentru păstrare: A se păstra la frigider (2ºC–8ºC). A nu se congela. A se păstra în ambalajul original pentru a fi protejat de lumină. Flaconul sigilat poate fi păstrat la o temperatură controlată a camerei de până la 25°C, cu lumină în încăpere, timp de până la 48 de ore. Natura și conținutul ambalajului: 4 ml, 10 ml, 12 ml sau 24 ml de concentrat în flacon a 10 ml sau 25 ml (sticlă de tip I) cu dop (butil-cauciuc) și capac de siguranță detașabil (aluminiu). Cutie cu 1 flacon. Precauții speciale pentru eliminarea reziduurilor și alte instrucțiuni de manipulare: Pregătirea trebuie efectuată de personal instruit în conformitate cu regulile de bună practică, în special în ceea ce privește condițiile aseptice. *Calcularea dozei:* Pentru administrarea dozei totale la un pacient, poate fi necesar mai mult de un flacon de OPDIVO concentrat. *Nivolumab în monoterapie:* Doza prescrisă pentru pacient este de 240 mg sau 480 mg în funcție de indicație, indiferent de greutatea corporală (vezi pct. 4.2 din RCP). *Nivolumab în asociere cu ipilimumab:* Doza prescrisă pentru pacient este exprimată în mg/kg. Pe baza acestei doze prescrise, se calculează doza totală care trebuie administrată. *Nivolumab în asociere cu ipilimumab pentru tratamentul MPM:* Doza prescrisă pentru pacient este de 360 mg, administrată indiferent de greutatea corporală. *Nivolumab în asociere cu chimioterapie:* Doza prescrisă pentru pacient este de 360 mg sau 240 mg, administrată indiferent de greutatea corporală. *Nivolumab în asociere cu ipilimumab și chimioterapie:* Doza prescrisă pentru pacient este de 360 mg, administrată indiferent de greutatea corporală. *Nivolumab în asociere cu cabozantinib:* Doza prescrisă pentru pacient este nivolumab 240 mg sau 480 mg, administrată indiferent de greutatea corporală. Vezi pct. 6.6, secțiunea „Pregătirea și administrarea", din RCP. Deținătorul autorizației de punere pe piață: Bristol-Myers Squibb Pharma EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Irlanda. Numărul(ele) autorizației de punere pe piață: EU/1/15/1014/001-004. Data primei autorizări: 19 Iunie 2015. Data ultimei reînnoiri a autorizației: 23 Aprilie 2020. Data revizuirii textului: Decembrie 2021. Informații detaliate privind acest medicament sunt disponibile pe site-ul Agenției Europene pentru Medicamente http://www.ema.europa.eu.

YERVOY (ipilimumab) - Informaţii esenţiale din rezumatul caracteristicilor produsului

Consultaţi Rezumatul Caracteristicilor Produsului (RCP) înainte de prescriere. **Compoziţia calitativă şi cantitativă:** Fiecare ml de concentrat conţine ipilimumab 5 mg. Ipilimumab este un anticorp monoclonal anti-CTLA-4 complet uman (IgG1κ). **Indicaţii terapeutice:** Melanom: YERVOY în monoterapie este indicat pentru tratamentul melanomului în stadii avansate (nerezecabil sau metastatic) la pacienţii adulţi, și adolescenți cu vârsta de 12 ani sau peste. YERVOY în asociere cu nivolumab este indicat pentru tratamentul melanomului în stadiu avansat (nerezecabil sau metastazat) la adulţi. În comparație cu monoterapia cu nivolumab, o creștere a supraviețuirii fără progresia bolii (SFP) și a supraviețuirii generale (SG) pentru asocierea nivolumab cu ipilimumab este stabilită numai la pacienții cu expresie tumorală redusă a PD-L1 (vezi pct. 4.4 și 5.1 din RCP). Carcinom renal (RCC): YERVOY în asociere cu nivolumab este indicat pentru tratamentul de primă linie al carcinomului renal avansat cu prognostic intermediar/nefavorabil, la adulți (vezi pct. 5.1 din RCP). Cancer bronho-pulmonar altul decât cel cu celule mici (NSCLC): YERVOY în asociere cu nivolumab și 2 cicluri de chimioterapie pe bază de săruri de platină este indicat pentru tratamentul de primă linie al cancerului bronho-pulmonar altul decât cel cu celule mici metastazat, la adulții ale căror tumori nu prezintă mutație sensibilizantă EGFR sau translocație ALK. Mezoteliom pleural malign (MPM): YERVOY în asociere cu nivolumab este indicat pentru tratamentul de primă linie al mezoteliomului pleural malign nerezecabil, la adulți. Cancer colorectal (CRC) cu deficiență de reparare a nepotrivirii ADN-ului (dMMR) sau cu instabilitate microsatelită de grad înalt (MSI-H): YERVOY în asociere cu nivolumab este indicat pentru tratamentul cancerului colorectal metastazat cu deficiență de reparare a nepotrivirii ADN-ului sau cu instabilitate microsatelită de grad înalt, după chimioterapie anterioară pe bază de asocieri de fluoropirimidine, la adulți (vezi pct. 5.1 din RCP). **Doze şi mod de administrare:** Doze: *YERVOY în monoterapie: Melanom:* Regimul de inducţie recomandat pentru YERVOY este de 3 mg/kg, administrat intravenos pe durata a 90 minute la fiecare 3 săptămâni pentru un total de 4 doze. Pacienţilor trebuie să li se administreze regimul complet de inducţie (4 doze) în funcţie de tolerabilitate, indiferent dacă apar leziuni noi sau dacă leziunile existente progresează. Evaluarea răspunsului tumoral trebuie efectuată doar după finalizarea terapiei de inducţie. *YERVOY în asociere cu nivolumab: Melanom:* Doza recomandată este de ipilimumab 3 mg/kg în asociere cu nivolumab 1 mg/kg, administrată intravenos la fiecare 3 săptămâni pentru primele 4 doze. Aceasta este urmată apoi de o a doua fază în care nivolumab este administrat în monoterapie pe cale intravenoasă fie în doză de 240 mg la fiecare 2 săptămâni **sau** în doză de 480 mg la fiecare 4 săptămâni. În faza de monoterapie, prima doză de nivolumab trebuie administrată: la interval de 3 săptămâni după ultima doză din terapia asociată nivolumab cu ipilimumab, dacă se utilizează doza de 240 mg la fiecare 2 săptămâni; sau la interval de 6 săptămâni după ultima doză din terapia asociată nivolumab cu ipilimumab, dacă se utilizează doza de 480 mg la fiecare 4 săptămâni (vezi, de asemenea, Tabelul 1 din RCP pentru duratele perfuziei); *Carcinom renal și cancer colorectal dMMR sau MSI-H:* Doza recomandată este de ipilimumab 1 mg/kg în asociere cu nivolumab 3 mg/kg, administrată intravenos la fiecare 3 săptămâni pentru primele 4 doze. Aceasta este urmată apoi de o a doua fază în care nivolumab este administrat în monoterapie pe cale intravenoasă fie în doză de 240 mg la fiecare 2 săptămâni **sau** în doză de 480 mg la fiecare 4 săptămâni (numai pentru RCC). În faza de monoterapie, prima doză de nivolumab trebuie administrată: la interval de 3 săptămâni după ultima doză din terapia asociată ipilimumab cu nivolumab, dacă se utilizează doza de 240 mg la fiecare 2 săptămâni; sau la interval de 6 săptămâni după ultima doză din terapia asociată ipilimumab cu nivolumab, dacă se utilizează doza de 480 mg la fiecare 4 săptămâni (numai pentru RCC) (vezi, de asemenea, Tabelul 2 din RCP pentru duratele perfuziei); *Mezoteliom pleural malign:* Doza recomandată este de 1 mg/kg ipilimumab administrat intravenos pe durata a 30 minute la fiecare 6 săptămâni în asociere cu 360 mg nivolumab administrat intravenos pe durata a 30 minute la fiecare 3 săptămâni. Tratamentul se continuă până la 24 luni la pacienții fără progresia bolii. *YERVOY în asociere cu nivolumab și chimioterapie: Cancer bronho-pulmonar altul decât cel cu celule mici:* Doza recomandată este de 1 mg/kg ipilimumab administrat intravenos pe durata a 30 minute la fiecare 6 săptămâni în asociere cu 360 mg nivolumab administrat intravenos pe durata a 30 minute la fiecare 3 săptămâni și chimioterapie pe bază de săruri de platină administrată la fiecare 3 săptămâni. După finalizarea a 2 cicluri de chimioterapie, tratamentul se continuă cu 1 mg/kg ipilimumab la fiecare 6 săptămâni în asociere cu 360 mg nivolumab administrat intravenos la fiecare 3 săptămâni. Tratamentul este recomandat până la progresia bolii, toxicitate inacceptabilă sau până la 24 luni la pacienții fără progresia bolii. *Durata tratamentului:* Tratamentul cu YERVOY în asociere cu nivolumab, trebuie continuat atât timp cât se observă beneficii clinice sau până când nu mai este tolerat de pacient (și până la durata maximă a terapiei, dacă este specificată pentru o indicație). S-au observat răspunsuri atipice (și anume, o creștere tranzitorie inițială a dimensiunii tumorii sau leziuni mici nou apărute în primele câteva luni, urmate de reducerea dimensiunilor tumorilor). La pacienții cu o stare clinică stabilă, care prezintă semne inițiale de progresie a bolii, se recomandă continuarea tratamentului cu YERVOY în asociere nivolumab, până la confirmarea progresiei bolii. Testele funcției hepatice (TFH) și testele funcţiei tiroidiene trebuie evaluate la momentul iniţial şi înaintea fiecărei doze de YERVOY. În plus, orice semne sau simptome de reacţii adverse mediate imun, inclusiv diaree şi colită, trebuie evaluate în timpul tratamentului cu YERVOY. Conduita terapeutică în cazul reacţiilor adverse mediate imun poate necesita întreruperea temporară a unei doze sau oprirea definitivă a terapiei cu YERVOY şi iniţierea corticoterapiei sistemice în doze mari. În unele cazuri, poate fi luată în considerare asocierea altei terapii imunosupresoare. Nu se recomandă creșterea sau scăderea dozelor. Poate fi necesară amânarea sau oprirea administrării tratamentului în funcţie de profilul individual de siguranţă şi tolerabilitate. Recomandările detaliate privind conduita terapeutică în cazul reacţiilor adverse mediate imun sunt prezentate la pct. 4.4 din RCP. Tratamentul cu YERVOY în asociere cu nivolumab trebuie oprit definitiv în caz de: reacții adverse de grad 4 sau reacții adverse recurente de grad 3; reacții adverse de grad 2 sau 3 persistente în pofida abordării terapeutice. Atunci când YERVOY este administrat în asociere cu nivolumab, dacă se întrerupe temporar administrarea oricăruia dintre aceste medicamente, se va întrerupe temporar şi administrarea celuilalt medicament. *Grupe speciale de pacienți: Copii şi adolescenţi:* Siguranţa şi eficacitatea YERVOY în monoterapie la copii cu vârsta sub 12 ani nu au fost stabilite. Foarte puține date sunt disponibile. YERVOY nu trebuie utilizat la copii cu vârsta sub 12 ani. Siguranța și eficacitatea YERVOY în asociere cu nivolumab la copii cu vârsta sub 18 ani nu au fost stabilite. Datele disponibile în prezent sunt prezentate la pct. 4.8 și 5.1 din RCP, dar nu se poate face nicio recomandare privind dozele. *Vârstnici:* În general, nu s-au raportat diferenţe în ceea ce priveşte siguranţa sau eficacitatea între pacienţii vârstnici (≥ 65 ani) şi cei mai tineri (< 65 ani). Datele provenite de la pacienții care urmează tratament de primă linie pentru RCC, cu vârsta de 75 ani sau peste, sunt prea limitate pentru a permite formularea unor concluzii referitoare la această grupă de pacienți (vezi pct. 5.1 din RCP). Nu sunt necesare ajustări specifice de doză. *Insuficienţă renală:* Nu sunt necesare ajustări specifice de doză la pacienții cu disfuncție renală ușoară până la moderată. *Insuficienţă hepatică:* Administrarea YERVOY se va efectua cu precauţie la pacienţii cu concentraţii plasmatice ale transaminazelor ≥ 5 x LSVN sau ale bilirubinei > 3 x LSVN înainte de iniţierea tratamentului. Mod de administrare: YERVOY se administrează intravenos. Durata perfuziei recomandată este de 30 sau 90 minute, în funcție de doză. YERVOY poate fi folosit pentru administrare intravenoasă fără diluare sau poate fi diluat cu soluție de clorură de sodiu 9 mg/ml (0,9%) pentru preparate injectabile sau cu soluție de glucoză 50 mg/ml (5%) pentru preparate injectabile până la concentraţii între 1 şi 4 mg/ml. YERVOY nu trebuie administrat intravenos rapid sau în bolus. Când se administrează în asociere cu nivolumab, sau în asociere cu nivolumab și chimioterapie, nivolumab trebuie administrat primul urmat de administrarea YERVOY și apoi de chimioterapie în aceeași zi. Pentru fiecare perfuzie se vor utiliza pungi și filtre pentru perfuzie diferite. Pentru instrucţiuni privind pregătirea și manipularea medicamentului înainte de administrare, vezi pct. 6.6 din RCP. **Contraindicaţii:** Hipersensibilitate la substanţa activă sau la oricare dintre excipienţii enumeraţi la pct. 6.1 din RCP. **Atenţionări şi precauţii speciale pentru utilizare:** Trasabilitate: Pentru a avea sub control trasabilitatea medicamentelor biologice, numele și numărul lotului medicamentului administrat trebuie înregistrate cu atenție. Ipilimumab în asociere cu nivolumab: Atunci când ipilimumab este administrat în asociere, se va consulta Rezumatul caracteristicilor produsului pentru celelalte componente ale terapiei asociate înainte de iniţierea tratamentului. Pentru informaţii suplimentare legate de atenţionări şi precauţii asociate tratamentului cu nivolumab, vă rugăm consultați RCP-ul pentru nivolumab. Majoritatea reacţiilor adverse mediate imun s-au ameliorat sau au ajuns la rezoluţie prin conduită terapeutică adecvată, inclusiv iniţierea corticoterapiei şi modificarea tratamentului. Reacţiile adverse mediate imun au survenit cu o frecvență mai mare atunci când nivolumab a fost administrat în asociere cu ipilimumab, comparativ cu utilizarea nivolumab în monoterapie. Reacții mediate imun: Tratamentul cu ipilimumab este asociat cu reacţii adverse inflamatorii care sunt rezultatul activităţii imune crescute sau excesive (reacţii adverse

mediate imun), corelată cel mai probabil cu mecanismul său de acţiune. Reacţiile adverse mediate imun, care pot fi severe sau care pun viaţa în pericol, pot apărea la nivelul aparatului digestiv, la nivel hepatic, cutanat, al sistemului nervos, endocrin sau la nivelul altor sisteme şi organe. Deşi majoritatea reacţiilor adverse mediate imun au apărut în perioada de inducţie, s-a raportat şi debutul acestora la câteva luni după administrarea ultimei doze de ipilimumab. Cu excepţia cazurilor în care se identifică o altă cauză, diareea, creşterea frecvenţei scaunelor, scaunele sangvinolente, creşterile valorilor TFH, erupţiile cutanate tranzitorii şi endocrinopatia trebuie considerate inflamatorii şi corelate cu terapia cu ipilimumab. Diagnosticul precoce şi conduita terapeutică adecvată sunt esenţiale pentru minimizarea complicaţiilor care pun viaţa în pericol. Recomandările specifice privind conduita terapeutică în cazul reacţiilor adverse mediate imun pentru utilizarea ipilimumab în monoterapie şi în asociere cu nivolumab: vezi RCP. Precauţii specifice afecţiunii: Pacienţi cu melanom ocular, melanom primar la nivelul SNC şi pacienţi cu metastaze cerebrale active nu au fost incluşi în studiul MDX010-20 (vezi pct. 5.1 din RCP). Reacţii legate de administrarea perfuziei: Pacienţii cu reacţii adverse uşoare sau moderate legate de administrarea perfuziei pot fi trataţi cu ipilimumab sau cu ipilimumab în asociere cu nivolumab sub supraveghere atentă. Premedicaţia cu medicamente antipiretice şi antihistaminice poate fi luată în considerare. Pacienţi cu boli autoimune: Ipilimumab poate interfera cu terapia imunosupresoare, ducând la exacerbarea afecţiunii subiacente sau la creşterea riscului de rejet al grefei. Administrarea ipilimumab trebuie evitată la pacienţii cu boli autoimune active severe în care activarea imună suplimentară se asociază cu potenţial iminent de a pune viaţa în pericol. La alţi pacienţi cu antecedente de boli autoimune, ipilimumab trebuie utilizat cu precauţie, după evaluarea atentă a raportului potențial risc-beneficiu pentru fiecare pacient în parte. Pacienţi care urmează o dietă cu restricţie de sodiu: YERVOY conţine sodiu. Acest lucru trebuie avut în vedere la pacienţii care urmează o dietă cu restricţie de sodiu. Administrare concomitentă, respectiv, Administrare secvenţială cu vemurafenib: vezi pct. 4.4 din RCP. **Interacţiuni cu alte medicamente şi alte forme de interacţiune:** Corticosteroizi: Administrarea corticoterapiei sistemice înainte de iniţierea terapiei cu ipilimumab trebuie evitată din cauza potenţialului de interacţiune cu activitatea şi eficacitatea farmacodinamică a acestuia din urmă. Cu toate acestea, corticoterapia sistemică sau terapia cu alte imunosupresoare poate fi utilizată după iniţierea ipilimumab pentru tratamentul reacţiilor adverse mediate imun. Anticoagulante: Deoarece hemoragia digestivă este o reacţie adversă asociată terapiei cu ipilimumab, pacienţii care necesită terapie anticoagulantă concomitentă trebuie monitorizaţi cu stricteţe. **Fertilitatea, sarcina şi alăptarea:** YERVOY nu este recomandat în timpul sarcinii sau la femei aflate la vârsta fertilă care nu utilizează măsuri contraceptive eficace, cu excepţia cazurilor în care beneficiile clinice depăşesc riscul potenţial. Din cauza potenţialului de a determina reacţii adverse la copiii alăptaţi, trebuie luată decizia fie de a întrerupe alăptarea, fie de a opri tratamentul cu YERVOY având în vedere beneficiul alăptării pentru copil şi beneficiul tratamentului pentru femeie. Nu se cunoaşte efectul ipilimumab asupra fertilităţii la femei şi bărbaţi. **Reacţii adverse:** Rezumatul profilului de siguranţă: *Ipilimumab în monoterapie: Foarte frecvente (≥ 1/10):* scăderea apetitului alimentar, diaree, vărsături, greaţă, erupţii cutanate tranzitorii, prurit, fatigabilitate, reacţii la locul administrării perfuziei, febră; *Frecvente (≥ 1/100 şi < 1/10):* durere tumorală, anemie, limfopenie, hipopituitarism (inclusiv hipofizită), hipotiroidism, deshidratare, hipopotasemie, stare de confuzie, neuropatie senzitivă periferică, ameţeli, cefalee, letargie, vedere înceţoşată, durere oculară, hipotensiune arterială, eritem facial tranzitor, bufeuri, dispnee, tuse, hemoragie gastrointestinală, colită, constipaţie, boală de reflux gastroesofagian, durere abdominală, inflamaţie a mucoaselor, anomalii ale funcţiei hepatice, dermatită, eritem, vitiligo, urticarie, eczemă, alopecie, transpiraţii nocturne, xerodermie, artralgie, mialgie, durere musculo-scheletică, spasm muscular, frisoane, astenie, edem, durere, afecţiune asemănătoare gripei, creşterea concentraţiei plasmatice a alanin aminotransferazei, creşterea concentraţiei plasmatice a aspartat aminotransferazei, creşterea concentraţiei plasmatice a fosfatazei alcaline, creşterea concentraţiei bilirubinei sanguine, scădere în greutate. *Ipilimumab în asociere cu nivolumab: Melanom:* În setul de date cumulat provenit din administrarea ipilimumab 3 mg/kg în asociere cu nivolumab 1 mg/kg la pacienţi cu melanom (n = 448), perioada minimă de monitorizare variind între 6 şi 28 luni, cele mai frecvente reacţii adverse (≥ 10%) au fost erupţiile cutanate tranzitorii (52%), fatigabilitatea (46%), diareea (43%), pruritul (36%), greaţa (26%), febra (19%), scăderea apetitului alimentar (16%), hipotiroidismul (16%), colita (15%), vărsăturile (14%), artralgia (13%), durerea abdominală (13%), cefaleea (11%) şi dispneea (10%). Majoritatea reacţiilor adverse au fost uşoare până la moderate (grad 1 sau 2). În rândul pacienţilor trataţi cu ipilimumab 3 mg/kg în asociere cu nivolumab 1 mg/kg în studiul CA209067, la 154/313 (49%) dintre aceştia primul debut al reacţiilor adverse de grad 3 sau 4 a avut loc pe durata fazei iniţiale de administrare asociată. Dintre cei 147 pacienţi din acest grup care au continuat tratamentul în faza de administrare a unui singur medicament, 47 (32%) au prezentat cel puţin o reacţie adversă de grad 3 sau 4 pe durata fazei de administrare a unui singur medicament. Pentru o perioadă de monitorizare de minim 60 luni a pacienţilor din studiul CA209067, nu au fost identificate noi semnale de siguranţă. *RCC și CRC dMMR sau MSI-H:* În setul de date cumulat provenit din administrarea ipilimumab 1 mg/kg în asociere cu nivolumab 3 mg/kg pentru multiple tipuri de tumori (n = 666), perioada minimă de monitorizare variind între 17,5 și 27,6 luni, cele mai frecvente reacții adverse (≥ 10%) au fost fatigabilitatea (58%), diareea (41%), durerea musculo-scheletică (39%), erupțiile cutanate tranzitorii (38%), pruritul (35%), greața (30%), tusea (29%), febra (29%), durerea abdominală (22%), artralgia (22%), scăderea apetitului alimentar (22%), infecțiile tractului respirator superior (21%), vărsăturile (21%), cefaleea (19%), dispneea (19%), hipotiroidismul (18%), constipația (18%), edemul (inclusiv edemul periferic) (16%), amețelile (14%), hipertiroidismul (12%), xerodermia (11%), hipertensiunea arterială (10%). Majoritatea reacţiilor adverse au fost uşoare până la moderate (grad 1 sau 2). În rândul pacienţilor trataţi cu ipilimumab 1 mg/kg în asociere cu nivolumab 3 mg/kg, la 194/666 (29%) dintre aceștia primul debut al reacţiilor adverse de grad 3 sau 4 a avut loc pe durata fazei inițiale de administrare asociată. Dintre cei 474 pacienți din acest grup care au continuat tratamentul în faza de administrare a nivolumab în monoterapie, 168 (35%) au prezentat cel puțin o reacție adversă de grad 3 sau 4 pe durata fazei de administrare a unui singur medicament. *MPM:* În setul de date provenit din administrarea ipilimumab 1 mg/kg în asociere cu nivolumab 3 mg/kg la pacienți cu MPM (n = 300), perioada minimă de monitorizare fiind de 22,1 luni, cele mai frecvente reacții adverse (≥ 10%) au fost fatigabilitatea (43%), diareea (31%), erupțiile cutanate tranzitorii (30%), durerea musculo scheletică (27%), greața (24%), scăderea apetitului alimentar (24%), pruritul (21%), constipația (19%) și hipotiroidismul (13%). Majoritatea reacţiilor adverse au fost uşoare până la moderate (grad 1 sau 2). *Ipilimumab în asociere cu nivolumab și chimioterapie (vezi pct. 4.2)* Atunci când ipilimumab este administrat în asociere, înainte de inițierea tratamentului se va consulta Rezumatul caracteristicilor produsului pentru componentele respective ale terapiei associate. În setul de date provenit din administrarea ipilimumab 1 mg/kg la fiecare 6 săptămâni în asociere cu nivolumab 360 mg la fiecare 3 săptămâni și 2 cicluri de chimioterapie în NSCLC (n = 358), perioada minimă de monitorizare fiind de 6,5 luni, cele mai frecvente reacții adverse au fost fatigabilitatea (36%), greața (26%), erupțiile cutanate tranzitorii (25%), diareea (20%), pruritul (18%), scăderea apetitului alimentar (16%), hipotiroidismul (15%) și vărsăturile (13%). Majoritatea reacțiilor adverse au fost ușoare până la moderate (grad 1 sau 2). Durata mediană a terapiei a fost de 6,1 luni (IÎ 95% 4,93, 7,06) pentru ipilimumab în asociere cu nivolumab și chimioterapie și de 2,4 luni (IÎ 95% 2,30, 2,83) pentru chimioterapie. Pentru informaţii complete privind reacţiile adverse, vezi RCP. Raportarea reacţiilor adverse suspectate: Profesioniştii din domeniul sănătăţii sunt rugaţi să raporteze orice reacţie adversă suspectată la: Agenţia Naţională a Medicamentului şi a Dispozitivelor Medicale, Str. Aviator Sănătescu nr. 48, sector 1, Bucureşti 011478- RO, Tel: + 4 0757 117 259, Fax: +4 0213 163 497, e-mail: adr@anm.ro. **Lista excipienţilor:** Vezi pct. 6.1 din RCP. **Incompatibilităţi:** În absenţa studiilor de compatibilitate, acest medicament nu trebuie amestecat cu alte medicamente. **Perioada de valabilitate:** Vezi pct. 6.3 din RCP. **Precauţii speciale pentru păstrare:** A se păstra la frigider (2°C-8°C). A nu se congela. A se păstra în ambalajul original pentru a fi protejat de lumină. Pentru condiţiile de păstrare a medicamentului după prima deschidere sau diluare, vezi pct. 6.3 din RCP. **Natura şi conţinutul ambalajului:** Cutie cu 1 flacon a 10 ml de concentrat. Cutie cu 1 flacon a 40 ml de concentrat. **Precauţii speciale pentru eliminarea reziduurilor şi alte instrucţiuni de manipulare:** Prepararea trebuie efectuată de personal instruit în conformitate cu reglementările de bună practică, în special în ceea ce priveşte condiţiile aseptice. **Deţinătorul autorizaţiei de punere pe piaţă:** Bristol-Myers Squibb Pharma EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Irlanda. **Data revizuirii textului:** Octombrie 2021. Informaţii detaliate privind acest medicament sunt disponibile pe site-ul Agenţiei Europene pentru Medicamente http://www.ema.europa.eu. Medicament eliberat pe bază de prescripţie medicală restrictivă: PR. Acest material promoţional este destinat profesioniştilor din domeniul sănătăţii.