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Cover: IMMUNE ARCHITECTURE OF HUMAN LUNG CANCER
Courtesy of Dr. Kurt Schalper, Associate Professor of Pathology and Medical Oncology, Yale University
Director of the Translational Immuno-oncology Laboratory, Yale Cancer Center.
The lung cancer tumor immune microenvironment. FFPE section from a lung carcinoma stained with a multiplexed immunofluorescence panel for simultaneous detection of DAPI (blue, all cells), pan-cytokeratin (green, tumor epithelial cells), CD4 (red, helper T-cells), CD8 (yellow, effector T-cells) and CD20 (white, B-lymphocytes). Tumor-infiltrating lymphocytes are predominantly located in the peritumoral stroma next to a tertiary lymphoid structure. Magnification 20x.

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

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Editorial

The 64th ASTRO Annual Meeting recently took place in San Antonio, Texas, USA, from the 23rd to the 26th of October 2022, in a successful hybrid form. The general theme was “Emotional & Artificial Intelligence (EI & AI)-Caring for the Patient in a Wireless Word”: very provocative and current. Telemedicine and artificial intelligence are already changing today’s Radiation Therapy landscape and will undoubtedly do even more so in the future. However, it is very likely that direct human contact between healthcare professionals and oncologic patients and their caregivers will remain a crucial pillar in the holistic process of cancer diagnosis, treatment and long-term follow-up.

In parallel to the outstanding progress in systemic therapy, particularly the latest developments in immuno-oncology, and the introduction of more potent and/or selective targeted molecular therapies, radiation therapy (RT) is evolving considerably. It is safely and efficiently delivered in more than 50 % of cancer patients, and in approximately half of them with curative intent. Among the current days’ attributes of modern complex RT are: higher precision, speed and comfort for patients, by reducing the total time of the RT (by hypofractionation or simultaneous integrated boost, for example for prostate or breast cancer).

Besides first calls or updated results of randomized clinical trials for various types of cancers, particular importance was given in the ASTRO 2022 program to the EDUCATION of ALL radiation oncology professionals to remain current with the state-of-the-art techniques, through dedicated sessions for physicians, physicists, technologists, and psychologists. In this setting, interactive and practical radiation oncology sessions were highly attractive, tackling the recently updated ASTRO guidelines in different cancers, such as brain or endometrial cancer.

Specific issues related to stereotactic RT were addressed during dedicated sessions for oligometastatic disease, lung, breast, digestive tract (in particular for pancreatic cancer and hepatocarcinoma), prostate and other types of cancer. Sarcomas, lymphomas, paediatric cancers and other rare cancers were not neglected, as well as particular techniques of RT such as Flash therapy, brachytherapy or targeted ligand binding irradiation.

Networking and direct interaction between institutions, professional associations, industry, sponsors, residents, specialists and experts from all over the globe were facilitated and highly encouraged, contributing to an engaging interdisciplinary forum-like experience, and opening further potential developments in the exciting field of high-quality radiation oncology, to mostly benefit patients and reducing social, ethnic, religious and geographic disparities and inequities.

Gabriel Kacsó, MD, PhD

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ASCO 2022 Breast Cancer Updates

Alida Podrumar[1]

[1] *Nassau University Medical Center, East Meadow, New York, USA*

Corresponding author: Alida Podrumar; **e-mail**: apodruma@numc.edu

Abstract

Data presented at ASCO 2022 provide new perspectives of therapy for patients with breast cancer. Starting with the plenary session with DESTINY-Breast04 we are turning a new page in the treatment of metastatic human epidermal growth factor receptor 2 (HER2)-low breast cancer patients. The results of the DESTINY-Breast04 trial open a new therapeutic option for half of the patients with metastatic breast cancer, establishing HER2-low metastatic breast cancer as a targetable population with trastuzumab deruxtecan. The indications for antibody drug conjugates are expanding to patients with metastatic hormone receptor positive endocrine resistant disease based on TROPICS-02. From the multitude of clinical trials with antibody drug conjugates, we can envision that this will be likely the new way to deliver chemotherapy in the future. Differences in survival within the three cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in upfront metastatic hormone positive breast cancer are emerging. We have data on continuation of ribociclib beyond disease progression on CDK4/6 in the MAINTAIN trial. The FAKTION trial does prove the benefit of the AKT inhibitor capivasertib and does highlight the importance of an extended molecular panel of the phosphatidylinositol3-kinase PI3K pathway. Furthermore, the exploratory analysis of KEYNOTE- 522, examining the correlation of event free survival and residual cancer burden after neoadjuvant treatment in patients with triple negative breast cancer does demonstrate a benefit of pembrolizumab extending to patient which did not achieve pathologic complete response, mainly by a decrease in residual cancer burden. Advances in biomarkers of response to immunotherapy are needed. For early stage breast cancer studies are in support of de-escalation of radiotherapy for low risk breast cancer patients and confirming the lack of benefit of adjuvant chemotherapy for elderly patients, even with high genomic grade index.

Keywords: *HER2 low breast cancer, antibody drug conjugates, CDK4/6 inhibitors, immunotherapy, triple negative breast cancer*

Review Articles

1. Introduction

This review will provide an overview of the most important clinical trials presented at ASCO 2022, discuss clinical implications and highlight some existing questions in the field. The treatment landscape of HER2-low metastatic breast cancer has changed. There are new developments for patients with endocrine sensitive hormone receptor positive breast cancer. The indications for antibody drug conjugates are extending from triple negative

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breast cancer (TNBC) to the endocrine resistant space. Historically TNBC has been difficult to treat. With first proven activity in the metastatic disease setting, the role of immune checkpoint inhibitors (ICI) in early stage TNBC has been recently established. Patients with residual disease after neoadjuvant chemotherapy are at the highest risk of relapse and continue to remain a therapeutic challenge.

2. HER2-low breast cancer

HER2-low is a breast cancer subgroup currently defined by immunohistochemical (IHC) analysis with IHC 1+ and 2 + in absence of HER2 gene amplification by fluorescent in situ hybridization (FISH) (1). It comprises approximately half of all breast cancers and is found more frequently in hormone receptor (HR) positive disease 63% than in HR-negative 34%[1,2]. A comparison of different molecular subtypes of breast cancer does show that the HR status is the major determinant of the biology of HER2-low breast cancer. The HR-positive subgroup is enriched with luminal subtypes, the HR-negative subtype is predominantly basal like (2).

While the HER2 expression in HER2-positive breast cancer is stable over time, studies have shown instability of HER2-low over time and a change of HER2 from low to zero and vice versa in the process of cancer progression to metastasis. This process did occur regardless of the HR status (3).

Regarding prognosis, no statistically significant differences in overall survival (OS) were observed between HER2-low and HER2-negative groups, prognosis being mostly dependent on HR status (2).

Historically only HER2-positive breast cancer did benefit from HER2 targeted therapy. Adjuvant Herceptin in patients with early stage HER2-low breast cancer was tested in the large, randomized phase III NSABP B47 trial enrolling 3270 patients with HER2-low breast cancer. One year of adjuvant trastuzumab plus chemotherapy vs. chemotherapy alone did unfortunately not improve disease-free survival (DFS) and OS (4).

Trastuzumab deruxtecan (T-DXd) is a new generation antibody drug conjugate (ADC) linking HER2 to the topoisomerase inhibitor deruxtecan (DXd), a diffusible cytotoxic moiety via a cleavable linker. One humanized monoclonal HER2 antibody is linked to this potent cytotoxic payload with a drug- antibody ratio of 8:1. When the ADC is internalized, the linker is cleaved by lysosomal enzymes, facilitating the cytotoxic effect chemotherapy. In comparison to trastuzumab-emtansine (TDM1), where DM1 is trapped inside the target cells, DXd is diffusible in the neighboring cells, being effective in tumor cells with lower degree of HER2 expression - the bystander effect (5,6).

DESTINY-Breast04 was the first randomized phase III multicenter trial for patients with HER2-low metastatic breast cancer. It did randomize 557 patients 2:1 to T-DXd vs physicians' choice of chemotherapy. Majority of patients (88.8%) were HR-positive and 11.3 % were HR-negative. All patients had a history of at least one prior chemotherapy but not more than two lines of chemotherapy. In the HR-positive patients the median progression free survival (PFS) was increased from 5.4 month to 10.1 month in the T-DXd arm with a hazard ratio of 0.51 and a $p < 0.0001$. Similar results were reported also in the entire group of patients with an improvement in median PFS from 5.1 to 9.9 month in the T-DXd group with a hazard ratio 0.5 and $p < 0.0001$, a 50% decrease in risk of disease progression. Among all patients there was a 6 month improvement in OS from 16.8 to 23.4 month with T-DXd hazard ratio 0.64 $p = 0.001$. A subgroup analysis did confirm the benefit in all patient categories: IHC 1+, IHC 2+, prior use of CDK 4/6, irrespective of the number of prior chemotherapies. Results of an exploratory analysis of the HR-negative HER2-low breast cancer group did also show an improvement in median PFS from 2.9 to 8.5 month with a hazard ratio of 0.46 (95% CI, 0.24 to 0.89) and a more than doubled median OS of 18.2 month hazard ratio of 0.48 (95% CI, 0.24-0.95) with T-DXd (7).

Regarding toxicity, interstitial lung disease (ILD) is included in the black box warning of this drug and did occur in 12.1% of patients within the T-DXd arm and 3 patients (0.8%) died of ILD. The median time to onset of ILD was 4-5 month into therapy (7). In DESTINY- Breast04 patients did undergo CT chest every 6 weeks,

a strategy difficult to implement in clinical practice. In clinic we have to focus on proactive monitoring of patient's pulmonary symptoms. ILD is treated per guidelines. Symptomatic ILD – grade 2 should lead to permanent discontinuation of T-DXd and prompt initiation of systemic corticosteroid treatment at 1 mg/kg/day prednisone for at least 14 days followed by a gradual taper over at least 4 weeks. For grade 1 asymptomatic ILD T-DXd is interrupted, steroids are started until ILD resolves to grade 0. If ILD resolves in ≤28 days from date of onset, the dose of T-DXd is maintained. If ILD resolves in >28 days from date of onset, T-DXd dose should be reduced by one dose level (8). On August 5, 2022, the Food and Drug Administration (FDA) approved T-DXd for patients with metastatic HER2-low breast cancer based on the positive results of DESTINY-Breast 04 trial results.

The concept of HER2-low continues to evolve. As per the data presented in DESTINY-Breast04 the level of HER2 expression by IHC 1+ vs 2+ did not correlate with treatment response. The DAISY trial is reporting a 30% response rates with T-DXd in patients with HER2 IHC 0 breast cancer [9], raising a critical question: which is the lowest level of HER2 expression associated with response to T-DXd? Can the effect of T-DXd in HER2- negative breast cancer patients be explained by the bystander effect? Do we need a more sensitive method than IHC to better select patients for T-DXd? It should be remembered that ASCO CAP guidelines define HER2 zero by less than 10% of cells with positive HER2 staining. The expression of HER2 on mass spectrometry is dependent on the level of IHC, but even IHC 0 has a low level of HER2 expression. The reported concordance among pathologist, especially in distinguishing between IHC 1+ and IHC 0 is as low as 26% (10).

Will list here few clinical trials being conducted in the HER2-low space. DESTINY-Breast06 is investigating upfront T-DXd in patients with HR-positive HER2 low metastatic breast cancer and includes a group of HER2-ultralow patients with IHC 0-1. Preclinical data suggest that HER2-positive tumors are immunogenic, enriched in tumor infiltrating lymphocytes (TIL) and have high level of programmed death-ligand 1 (PDL1) expression (11,12). In order to further improve the treatment and prognosis of HR-negative HER-2 low patients, a group of patients with poor prognosis, DESTINY- Breast08 is studying the combination of T-DXd with immunotherapy (IO). The TALENT trial is the first neoadjuvant trial with T-DXd and endocrine therapy with a pathologic complete response (pCR) endpoint [13].Given the reported activity in the brain of T-DXd in HER2-positive breast cancer (14), T-DXd activity in patients for HER2-low with brain metastasis is being analyzed in the DEBRA trial.

3. HER3 positive breast cancer

Another target is HER3, expressed in up to 30-50% of breast cancers and associated with a poor prognosis (15). Historically given the lack of the kinase domain, HER3 cannot be targeted with tyrosine kinase inhibitors and HER3 directed monoclonal antibodies have limited activity. Dr. Krop was reporting at ASCO 2022 results of the phase 1/2 study of patritumab deruxtecan in HER3 expressing metastatic breast cancer. Analysis of 118 patients, 113 HR-positive, 53 HR-negative and 43 HER2-positive did report an overall response rate (ORR) of 30% in HR-positive/HER2 negative, 22.6 % in HR-negative and 42.9% HER2-positive patients with a median PFS of 7.4 month in HR-positive, 5.5 month in HR-negative and 11 month in HER2-positive breast cancer patients. A direct relationship between HER3 expression and patritumab deruxtecan activity could not be demonstrated. The mechanism of action of patritumab deruxtecan in the HER3 low patients is not very well understood and could be explained by the ADC potency, bystander effect and high drug to antibody ratio. Regarding safety, the most common toxicities observed were gastrointestinal and hematologic with neutropenia and thrombo-cytopenia. ILD did occur in 6.6% of patients; although primarily grade 1 and 2, there was one fatal ILD event (16).

4. Metastatic HR-positive breast cancer

While a cross trial comparison shows similar PFS with the three cyclin- dependent kinase 4 and 6 (CDK4/6) inhibitors in first line metastatic breast cancer when combined with

aromatase inhibitors, ribocilcib is reporting OS (17), including in combination with fulvestrant (18).The final OS analysis of the addition of pabociclib to frontline letrozole in postmenopausal women with HR-positive HER2-negative breast cancer patients in PALOMA -2 concluded that the addition of palbociclib to letrozole did not significantly improve OS. The median OS in both arms was around 50 months. Given the long follow up on this trial, with a median of 90 months, patients were lost for follow-up and survival data were missing (19). How should we interpret these differences? Is one CDK4/6 inhibitor better than the other? Mature OS data of Monarch 3 trial with upfront abemaciclib and aromatase inhibitor are expected in 2023. A second interim analysis of the Monarch 3 trial presented at ESMO 2022 does show a favorable OS, although with no statistical significance (20). In clinic a discussion with the patient should reflect these differences in efficacy as well as differences in toxicity profile.

The treatment of patients progressing on first line CDK4/6 endocrine therapy raises important questions, including the benefit of continuation of the CDK 4/6 after disease progression. The MAINTAIN trial, a multicenter randomized, placebo-controlled phase II trial of 120 patients found a significant PFS benefit with a median PFS increase from 2.8 month to 5.3 month and a hazard ratio of 0.57 (95% CI: 0.39-0.95) p=0.006 when patients with HR-positive HER2-negative metastatic breast cancer changed endocrine therapy and received ribociclib following progression on CDK4/6 inhibitor. Most patients had previously received palbociclib. PFS was seen in all subgroups independent of the prior duration of the CDK 4/6, presence of visceral metastasis (21). How are we going to use this data for our patients in clinic? With the change of the endocrine therapy and the CDK4/6 inhibitor at the same time, it is difficult to clearly discern the contribution of ribociclib as the second CDK 4/6 inhibitor. PADA-1 trial data [22],while changing the endocrine partner by using serial estrogen receptor 1 (ESR1) mutation tracking, is also providing evidence for CDK 4/6 maintenance. Continuation of ribociclib could be an option in the absence of PIK3CA mutations, in patients with a slow disease progression. For more date we are awaiting the results of the Capitello 291 trial with the AKT inhibitor capivasertib and fulvestrant vs fulvestrant in patients with metastatic HR-positive breast cancer with progression on AI and CDK 4/6. In order to further redefine the importance of molecular alterations, a subset analysis of patients with PIK3CA/AKT1/PTEN alteration is planned in this study (23).

Although may be with less clinical impact, since patients with prior treatment with CDK4/6 inhibitors were not included, the phase II FAKTION study of fulvestrant plus capivasertib or placebo after progression on aromatase inhibitors is drawing attention to the importance of an expanded group of molecular markers PIK3CA activating mutations, AKT1 E17K mutation and PTEN alterations on next generation sequencing (NGS) or plasma by circulating tumor DNA (ctDNA).The expanded testing did identify pathway alterations in 25% of patients initially classified as nutation negative. In patients with pathway alterations capivasetib and fulvestrant was associated with an improvement in median PFS of 12.8 month vs 4.6 month with fulvestrant and placebo, hazard ratio of 0.44 (95%CI:0.26-0.72 p=0.0014) and an improvement in median survival of 38.9 month vs 20 month with a hazard ratio 0.46 (95% CI:0.27-0.79) p=0.0047 (24).

5. New antibody drug conjugate data

TROPICS-02 Phase III Trial is the first trial to investigate an ADC in HR-positive patients, refractory to endocrine therapy. It did evaluate the ADC sacituzumab govitecan in HR-positive HER2-negative heavily pretreated metastatic breast cancer patients with progression on endocrine therapy, two to four prior lines of chemotherapy and 85% of liver metastasis. This trial is reporting a median PFS of 5.5 month with sacituzumab govitecan vs 4 month in the physician's choice chemotherapy with a hazard ratio 0.66 (95% CI :0.53-0.83) p=0.0003. Although the improvement does seem to be modest the analysis at 6, 9 and 12 month shows an increase in the percentage of patients free of progression with a flattening of the PFS curves and a tripling of number of patients progression free at 1 year (25). OS was updated at ESMO 2022 with a median OS of

benefit of 3.2 month OS in favour of sacituzumab govitecan hazard ratio 0.79 (95% CI: 0.65-0.96; *P* = .02) (26).

There are now two ADC with activity in metastatic HR-positive breast cancer resistant to endocrine therapy. Data comparing sacituzumab govitecan and trastuzumab deruxtecan are not available. Sacituzumab govitecan was added to the National Comprehensive Cancer Network (NCCN) as a treatment option for patients with HR-positive HER2-negative patients with disease progression on prior endocrine therapy, CDK4/6 inhibitors and at least two lines of chemotherapy (including taxanes), reinforcing the clinical activity of this treatment in a patient population where the need is the highest.

6. Early stage triple negative breast cancer

The phase III Keynote-522 trial led to the FDA approval of pembrolizumab in the neoadjuvant therapy of early-stage breast TNBC based on benefit in pCR and event free survival (EFS). 1174 patients with stage II or III TNBC were randomized in a 2:1 ratio to neoadjuvant therapy with four cycles of pembrolizumab or placebo every 3 weeks plus paclitaxel and carboplatin, followed by four cycles of pembrolizumab or placebo plus anthracycline- cyclophosphamide. After surgery patients did continue adjuvant pembrolizumab or placebo for a total duration of one year of therapy. In a final analysis the improvement in pCR was 7.5% (95% CI 1.6-13.4) in the pembrolizumab arm (27). A clinically and statistically significant 3-year EFS improvement from 76.8% to 84.5% hazard ratio 0.63 (95% CI, 0.48–0.82; *P*<.001) was observed in the control versus pembrolizumab arm (28) and led to the FDA approval of pembrolizumab for neoadjuvant therapy in early stage TNBC on July 26, 2021.

At ASCO 2022 Dr. Pusztai did present an exploratory analysis of EFS by residual cancer burden (RCB) categories showing that the benefit of pembrolizumab is extending beyond the increase in pCR, by the effect of pembrolizumab in decreasing the RCB. The greatest benefit of pembrolizumab was seen in patients in the RCB-2 group. Patients with RCB-2 had an improvement in EFS of 75.7% vs 55.9% with placebo (HR 0.52; 95% CI: 0.32-0.82). Patients with RCB-0 and RCB-1 had very high 3-year EFS in both treatment arms and no statistically significant benefit for pembrolizumab was seen in these groups. Among patients with RCB-3, there was also no difference in 3 years of EFS, this group of patients representing likely a group of patients with primary refractory disease with no benefit of ICI (29).

Few clinical considerations merit further attention: To what extent does the chemotherapy regimen affect the responses to the neoadjuvant treatment? While different chemotherapy back-bones have been used in different neoadjuvant studies, KEYNOTE- 522 regimen is the only study reporting outcomes, combining neoadjuvant carboplatin and anthracycline. Do we need both, do we need carboplatin or can an anthracycline free regimen be used? Impassion 031 and GeparNUEVO used a platinum based neoadjuvant chemoimmunotherapy regimen with favorable EFS results (30,31). The use of an anthracycline free, less toxic regimen is still controversial. Omission of anthracyclines in NeoTRIPaPD-1 trial led to no improvement in pCR with nab-paclitaxel/carboplatin/atezolizumab when compared to chemotherapy alone (32), suggesting that anthracyclines may lead to upregulation of the immune-related genes, resulting in a favorable tumor microenvironment (TME) (33). The benefit on pCR and safety of platinum-based, anthracycline free combination in neoadjuvant setting in the NeoSTOP trial (34), is further confirmed in the NeoPACT trial with the addition of pembrolizumab to carboplatin /docetaxel in the neoadjuvant setting, reporting a pCR of 58% (95%CI: 51-70%) and 2-year EFS of 89% (35).

Is adjuvant pembrolizumab needed in patients achieving a pCR to neoadjuvant therapy? GeparNUEVO did not use immunotherapy in the adjuvant part of the treatment course and is also reporting improvement of EFS (30). The planned OptimICE- pCR trial is expecting to answer this question.

What is the best treatment of residual disease? KEYNOTE-522 did not include capecitabine treatment for residual disease. Considering the CREATE-X trial reported improvement in 5-year DFS 69.8% for capecitabine vs. 56.1% for observation with a hazard ratio

0.58 (95%CI 0.39-0.87) and OS 78.8% vs 70.3% hazard ratio 0.52 (95%CI 0.3-0.9) by escalation of post-neoadjuvant treatment with the addition of 4-6 cycles of adjuvant capecitabine (36), adjuvant capecitabine should be recommended for residual disease. Although capecitabine and pembrolizumab have overlapping toxicities, no major adverse side effects were mentioned with this combination. How can the OlympiA PARP inhibitor data in patients with gBRCA1 and gBRCA2 with residual disease be integrated in this treatment? We need to mention that OlympiA study did not include neoadjuvant IO and adjuvant olaparib was also not part of KEYNOTE-522. Supported by the benefit of adjuvant olaparib in gBRCA patients in OlympiA (37,38), the safety of the combination of olaparib and pembrolizumab, this combination should be recommended for patients with residual disease and gBRCA. Promising efficacy results of PARP inhibitors in metastatic breast cancer in patients with PALB2 and somatic BRCA mutation (39), might lead to the future use of PARP inhibitors in these mutations in early-stage disease.

PD-L1 status was not predictive of benefit for neoadjuvant pembrolizumab in the KEYNOTE-522 trial. While stromal and intra tumoral TIL have been confirmed to have prognostic value and are predictive of a good response to neoadjuvant therapy across multiple trials (40), there are not able to predict the response to the addition of ICI (30,31). A 27 gene -immunomodulatory signature score assay reported in a post hoc analysis NeoTRPaPDL1 is correlating with response to ICI (41). Emerging clinical trials are using TIL, to select patients for chemotherapy de-escalation strategies (42). In addition to the number of TIL the spatial relationship of the TIL with the cancer is a predictor of response to ICI. Currently following subgroups of tumor immune microenvironment are being described: the “immune deserted” subtype characterized by a low number of CD8 T cells, the “margin restricted” subtype with CD8 T cells restricted to tumor margins and fibrosis, the “inflamed “subtype displaying CD8 T cells within the epithelium and stroma, and the “stromal restricted” subtype with CD8 T cells restricted to the stroma (43). A better understanding of the tumor immune micro-environment may lead to better selection of patients able to benefit from immunotherapy. The impact of the gut microbiome composition on the response to neoadjuvant treatment in early stage TNBC is an emergent field of research (44). Recent publications show that patients exhibiting plasma circulating tumor DNA (ctDNA) after treatment for early-stage breast cancer have a worst prognosis and are more likely to relapse (45). Identification of ctDNA as a marker of minimal residual disease and its potential use to in an adaptive treatment approach is being investigated in ongoing clinical trials (46).

7. Early-stage HR-positive breast cancer

The prognosis of patients with early-stage low risk HR-positive breast cancer is very good and overtreatment of this patients should be avoided. LUMINA trial is a phase III study of 500 patients 55 years or older with invasive ductal cancer stage I HR-positive, luminal A, defined as ER≥1%, PR >20 %, HER2-negative and Ki 67 ≤13.25%, grade 1 or 2, omitting radiation therapy after lumpectomy, sentinel node biopsy and endocrine therapy. The study is reporting a 5 year follow up a with a 2.3% local recurrence rate, concluding that patients with low-risk breast cancer can forgo radiation therapy after breast conserving surgery and endocrine therapy (47). Can we now omit radiation therapy? Ki 67 reproducibility is of concern and clinical trials using genomic signatures to guide omission of radiation for patients with low-risk breast cancers are ongoing. LUMINA provides further evidence of omitting radiation therapy in elderly patients, but the safety of omitting radiation therapy in younger patients with longer life expectancy is still to be confirmed in additional studies.

The phase III randomized ASTER 70s trial for patients more than 70 years of age with early-stage HR-positive tumors, high genomic grade index, did confirm that there was no benefit for adjuvant chemotherapy, providing additional evidence to an existing literature that older patients get no benefit from chemotherapy, even with high genomic grade index (48).

Regarding adjuvant denosumab, a long-term follow-up from the ABCSG-18 trial does provide evidence that addition of denosumab during adjuvant aromatase inhibitor therapy does lower the rate of fractures and is also associated with an improved bone metastases-free survival by 19% and OS by 20%[49]. The previously reported D-CARE trial with adjuvant denosumab did not show any benefit of denosumab in prevention of breast cancer recurrences but did include a higher risk patient population and HR-negative patients and [50]. The ABSCG-18 study findings are similar to the results with bisphosphonates, which are currently the guideline-recommended standard of care for bone-strengthening adjuvant treatment for early-stage breast cancer and therefore denosumab can be considered as adjuvant therapy for postmenopausal HR-positive patients.

8. Conclusions:

Last ASCO draws attention to numerous advances in the management of patient with breast cancer, the most notable one being the paradigm shift in the treatment of HER2-low breast cancer. The HER2-low landscape is continuing to evolve, the optimal cutoff predicting response to T-DXd is unfolding. We have much to learn on sequencing ADC, as more are available for use in our patients. We expect further data in the post CDK4/6 inhibitor space for HR-positive metastatic breast cancer. Further research is needed to establish how to best select patients who benefit from immunotherapy.

Abbreviations:

ADC – antibody drug conjugate
AKT – protein kinase B
CDK4/6 – cyclin dependent kinase 4/6
ctDNA – circulating tumor DNA
DFS – disease free survival
EFS – event free survival
ESR1 – estrogen receptor 1
FDA – Food and Drug Administration
FISH – fluorescent in situ hybridization
HER – human epidermal receptor
HR – hormon receptor
IHC – immunohistochemistry
ILD – interstitial lung disease
NCCN – National Comprehensive Cancer Network
NGS – next generation sequencing
PALB2 – partner and localizer of BRCA2
PARP – poly (adenosine diphosphate-ribose) polymerase
PCR – pathologic complete response
PDL1 – programmed death ligand 1
PIK3CA – phosphatidylinositol 3-kinase
PTEN – phosphatase and tensin homolog
ORR – overall response rate
OS – overall survival
TDXD – trastuzumab deruxtecan
TDM1 – trastuzumab emtansine
TIL – tumor infiltrating lymphocytes

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Nutritional Support Indications in Patients with Gastroesophageal Cancer: A Review

Ludovica Gandullia[1], Irina Mihaela Cazacu[2], Vlad Mihai Croitoru[2], Paolo Gandullia[3]

[1] *Faculty of Medicine, Titu Maiorescu University, Bucharest, Romania*
[2] *Department of Oncology, Fundeni Clinical Institute, Bucharest*
[3] *Pediatric Gastroenterology and Endoscopy Unit, Integrated Department of Pediatric and Hemato-Oncological Sciences, IRCCS "G. Gaslini" Children's Hospital, Genoa, Italy*

Corresponding author: Ludovica Gandullia; **e-mail**: ludovicagandullia.lg@gmail.com

Abstract

Nutritional support is an essential part of cancer care. Malnutrition is a common feature in cancer patients and has a negative impact on the quality of life and treatment tolerance. Patients with digestive cancers are at higher risk of malnutrition due to the gastrointestinal impairment caused by their disease. However, most of them have insufficient access to nutritional support.

Early identification of patients at risk of malnutrition is crucial in order to start an adequate nutritional support. Robust evidence showed that nutritional support can reduce length of hospitalisation, decrease treatment-related toxicity, and improve quality of life and physical function. Nutritional intervention can improve outcomes and help patients in the successful completion of oncological treatments by preventing malnutrition. The aim of this review is to provide a comprehensive overview of nutritional interventions for patients with gastroesophageal cancers.

Keywords: *nutrition, gastrointestinal cancer, oral enteral nutrition, parenteral nutrition*

Review Articles

1. Introduction

Malnutrition is a common feature in cancer patients and is the consequence of both the presence of the tumor and anticancer treatments. Almost one-fourth of cancer patients are at risk of dying because of malnutrition, rather than cancer itself (1). Moreover, malnutrition negatively impacts their quality of life and treatment toxicities (2).

Nutrition is considered a supportive therapy for cancer patients. Robust evidence indicates the benefits of professional nutritional support in improving nutrient intake, quality of life, and physical function in oncological patients (3, 4).

Experts recommend routinely using a nutritional screening, at diagnosis and throughout the course of disease, for detecting the risk of malnutrition and, if it is positive, to perform a complete nutritional assessment (5). There are

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different screening tools and methods to detect the nutritional risk. The nutritional needs of the cancer patients, except in those cases where individualized measures are required, should be considered similar to healthy individuals (i.e. 25–30 kcal/kg/day). The nutritional monitoring of the cancer patient should be multidisciplinary. Parenteral nutrition (PN) is indicated mainly when it is not possible to use the digestive tract and/or oral feeding and/or enteral nutrition is not sufficient or possible (5).

Patients with digestive cancers are at higher risk of suffering of malnutrition due to the gastrointestinal impairment caused by their disease. The aim of this review is to provide a comprehensive overview of nutritional interventions for patients with gastroesophageal cancers.

2. Nutritional Status and Cancer Outcomes

Malnutrition, as defined by the World Health Organization (WHO), refers to deficiencies, excesses, or imbalances in a person's intake of energy and/or nutrients. Malnutrition adversely affects the evolution of cancer patients, increasing the incidence of infections, length of hospital stays, and risk of death (6, 7).

Patients with cancer often have important nutritional deficiencies that significantly affect their quality of life (Table 1). In fact, the proportion of patients who at the time of diagnosis present with weight loss, ranges from 15 to 40% depending on the type of cancer (8).

According to the Spanish study NUPAC (9), the prevalence of moderate and severe malnutrition in patients with advanced cancer was 52%. Additionally, the incidence of malnutrition increases as the disease progresses until it affects 80% of patients (9).

Furthermore, malnutrition had an impact on hospital stay and costs, with an average stay of 3–4 days for malnourished patients, as compared to well-nourished ones and an increase in costs associated with hospitalization of 20–25% (10).

Malnutrition negatively impacts quality of life and treatment toxicities, and it has been estimated that up to 10-20% of cancer patients die due to consequences of malnutrition rather than due to the cancer itself (5).

A nutritional assessment is recommended for all cancer patients at diagnosis and during the treatment period in order to detect malnourished patients and to carry out an early intervention, since late diagnosis may make it difficult to recover and gain weight (11).

The ESPEN (European Society for Clinical Nutrition and Metabolism) guidelines, published in 2017 recommend periodically assessing nutrient intakes, weight, and body mass index (BMI), starting at the cancer diagnosis and with repeat evaluations based on the stability of the clinical situation (5).

Table 1. Causes Associated with Malnutrition in Cancer Patients (12)

Tumor	**Mechanical and functional alterations**
	The release of catabolic hormones, cytokines and mobilizing factors that favour hypermetabolism and cachexia
Patient	Personal habits, physical deterioration, anorexia and psychological factors
Treatment	Side effects of the surgery, radiotherapy, chemotherapy and immunotherapy. Mucositis, emesis and diarrhea make intake difficult and favor malabsorption and loss of nutrients
Medical staff	Lack of nutritional assessment, poor knowledge, and training to detect malnutrition, delay in initiating adequate enteral and parenteral nutrition
Health authorities	Absence of a professional planning
	Deficit in the Nutrition Units and dietitians in the hospitals' organigrams

3. Screening for Nutritional Status

3.1. Screening tools

The most frequent nutritional screening tools used in clinical practice are the following:

1. for hospitalized patients: Nutritional Risk Screening 2002 (NRS 2002) (13)

2. for the general population: the malnutrition universal screening tool (MUST) (14)

3. for the elderly patient, the mini nutritional assessment (MNA) (15) and the malnutrition screening tool (MST) (16) have been validated in hospitalized patients and outpatients on chemotherapy and radiation therapy.

In the Multidisciplinary Clinical Guidelines on Nutrition Management of the Cancer Patient published in Spain in 2008 (17), it was agreed to use MST as a nutritional screening for adult patients with cancer for its simplicity, reliability, and validity. The MST is composed of two questions: one related to weight loss and the other one to intake/appetite. Patients were classified into two groups: at risk of malnutrition (score ≥2) and without risk of malnutrition (score <2). Once the risk of malnutrition is detected, a complete nutritional assessment is required.

The most frequently used tool for nutritional assessment is the SGA-GP (subjective global rating generated by the patient) (18). It includes information on medical history (weight loss, dietary habits, gastrointestinal impairment) and physical examination (muscle mass, subcutaneous fat, edema). It also involves the patient himself who completes the part regarding the symptoms, the type of diet, and their daily activity. This classifies the patient into: (a) normonutrite, (b) at nutritional risk or moderate malnutrition and (c) severe malnutrition (18).

A combination of several clinical, analytical, anthropometric, and functional parameters should be considered to assess the initial and follow-up nutritional status of cancer patients (18). Clinical parameters, such as the tumor location (there is a greater nutritional risk in the digestive tract cancer) and the treatment received (greater risk with the use of concomitant treatments) have been identified together with the detection of signs such as anorexia, asthenia, decreased physical activity, nausea, diarrhea, steatorrhea or constipation, dysgeusia, pain, depression, or socioeconomic problems that hinder access to the food (12). The ESPEN guidelines recommend an assessment of muscle mass and fat reserves that can be performed by dual X-ray absorptiometry (DEXA) or bioimpedance analysis (BIA), as well as an assessment of physical performance using various scales such as the ECOG or Karnofsky score (5).

The analytical parameters frequently associated with nutritional status are C reactive protein, albumin and prealbumin; however, they should be evaluated in the global context as they can be altered by other intercurrent and common problems in cancer patients. The ESPEN guidelines recommend the use of serum C-reactive protein (CRP) and albumin to measure systemic inflammation (5, 19).

Among the anthropometric parameters, significant weight loss defined as more than 10% in 6 months or 5% in3 months are considered the most reliable indicator of nutritional deficit. Another accessible anthropometric indicator is the measurement of the brachial circumference, as a method to evaluate for muscle mass loss. A measurement of less than 20 cm or a decrease of more than 2 cm between two determinations, suggests malnutrition (5). Other more precise tools are not available.

3.2. Indication of nutritional support

Nutritional support is classified according to its aggressiveness and complexity, and the following methods are included:

A. Nutritional recommendations and hygienic-dietary advice.

B. Artificial nutrition:

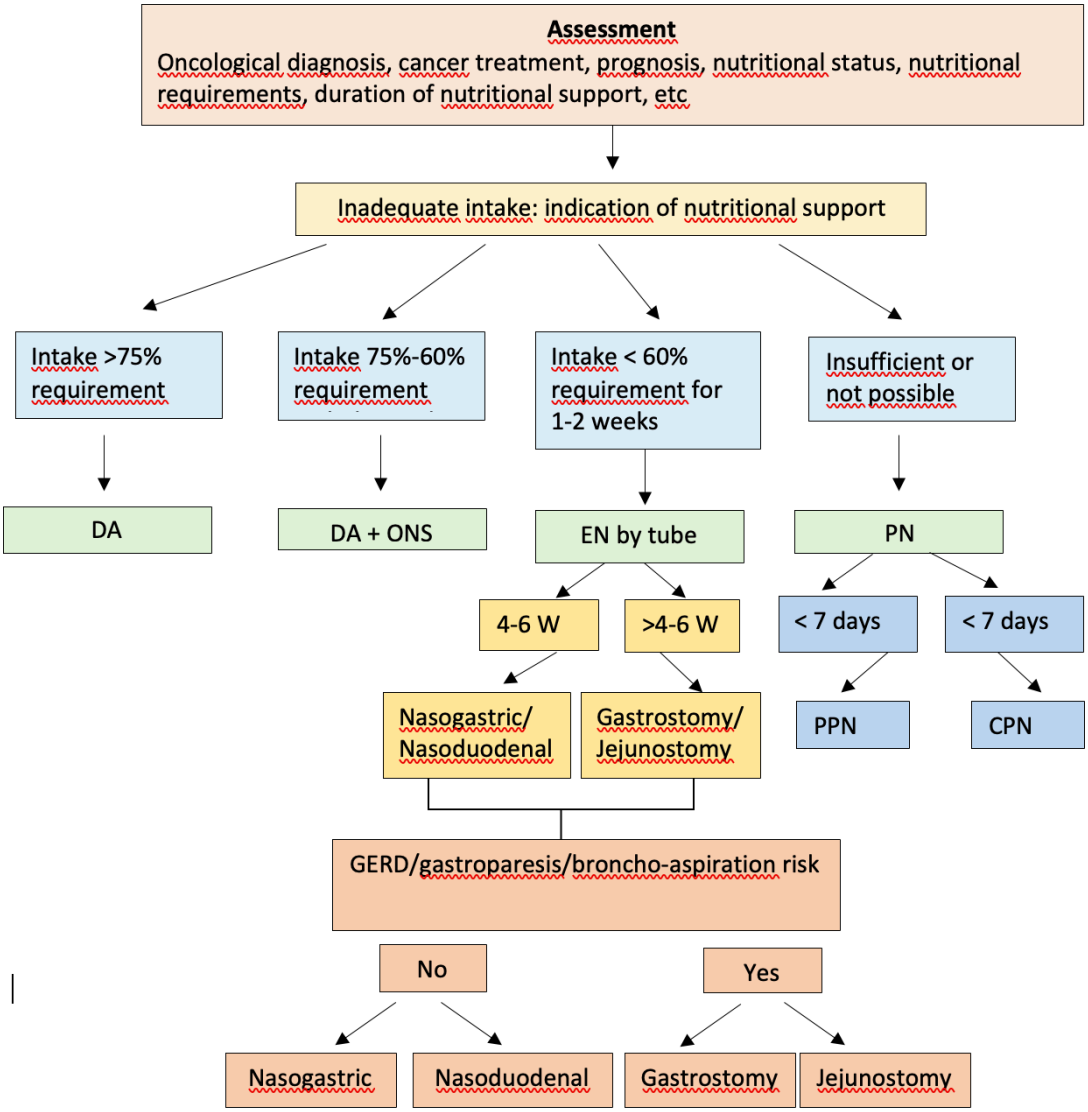
a. Supplementation with oral enteral nutrition (ONS).

b. Enteral nutrition by tube.

c. Parenteral nutrition (PN).

The method of choice depends on the patient's current situation: oncologic diagnosis, cancer treatment, prognosis, nutritional status, nutritional requirements, and duration of nutritional support **(Figure 1)**. In cancer patients, nutritional support is indicated when there is malnutrition, the patient is not expected to be able to eat food for a week or more, or if their intake is less than 60% of their needs for more than 10 days (5).

Figure 1. Nutritional Support Algorithm (Adapted from Hernàndez et al.(17))



DA dietetic advice. ONS oral nutritional supplements. EN enteral nutrition. PN parenteral nutrition. W weeks. NasoEnt nasoenteral. PPN peripheral parenteral nutrition. CPN central parenteral nutrition. GERD gastro esophageal reflux disease.

3.3. Nutritional requirements in cancer patients

The energetic requirements of cancer patients should be considered similar to those of healthy people (25–30 kcal/kg/day), if individualized measures are not performed (12, 20). It should be taken into consideration that this approach is often overestimated in obese people and underestimated particularly in thin patients. Protein requirements are advised to be between 1 (minimum) and 1.2–1.5 g/kg/day and if there is protein catabolism it can be increased to 2 g/kg/day (12). The ideal lipid/carbohydrate ratio will be determined by the clinical situation or medical history of each patient. If there is insulin resistance it is recommended for this relationship to shift in favour of lipids, because of increased glucose oxidation and weight loss (12).

It is also important to take into consideration the water and sodium needs, which should be below normal (30 ml/kg/day for water and 1 mmol/kg/day for sodium) in the case of peritoneal carcinomatosis with obstruction or ascites, for avoiding overload or third space (5, 12).

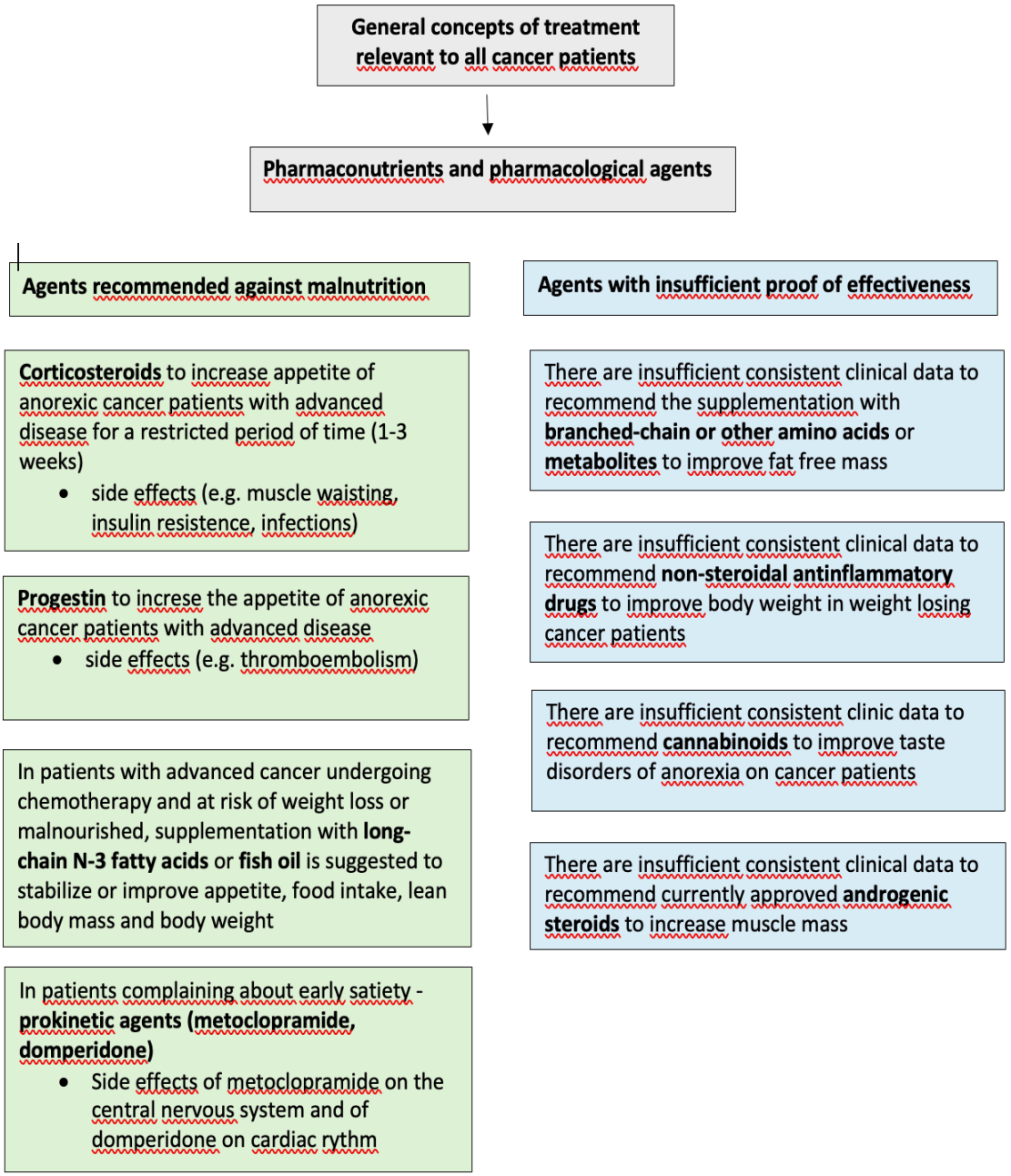
Regarding vitamins and trace elements, if there are no specified deficits it is not suggested to supplement in amounts higher than the recommended daily doses (5, 12)

3.4. Pharmaconutrition

The specific nutrients or ''pharmaconutrients'' are nutritional substrates that in addition to their nutritional value have other benefits for the organism. They are used to modulate the course of the disease, for example, omega 3 fatty acids, arginine, or glutamine. ESPEN guidelines suggest using supplementation only of omega 3 fatty acids in advanced cancer patients to stabilize or improve appetite, food intake, lean body and body weight (5).

The pharmaconutrients and pharmacological agents recommended by ESPEN for cancer patients are summarized in Figure 2 (5).

Figure 2. Pharmaconutrients and Pharmacological Agents Used for Nutritional Support in Cancer Patients (Adapted from Arends et al. (5))



3.5. Indications of parenteral nutrition

PN, as a specific nutritional support modality in the cancer patients, is indicated mainly when it is not possible to use the digestive tract and/or oral feeding and/or enteral nutrition is not sufficient or possible.

The main indications of PN in cancer patients are the following:

a. Difficult access to the digestive tract: perforation, intestinal obstruction, or chylothorax

b. Impossibility of access to the digestive tract: high-throughput entero-cutaneous fistulas, paralytic ileus, digestive haemorrhage, or insufficient absorptive surface

c. Ineffective digestive tract: short bowel syndrome, high-throughput fistulas, intestinal insufficiency due to radiation-induced enteritis

d. Low oral and/or enteral intake: less than 60% of the nutritional needs for more than 1–2 weeks and an improvement in the nutritional status and quality of life is foreseen.

When the estimated survival is greater than 1–3 months, and in case of intestinal insufficiency, PN can be offered, if the oral/enteral route is insufficient and there are expectations of improvement in the patient's quality of life and functionality and with an express desire of this one (5).

4. Nutritional Support Strategies for Patients with Early-Stage Gastroesophageal Cancer (resectable)

According to ESPEN guidelines (5), all cancer patients undergoing either curative or palliative surgery should be managed within an enhanced recovery after surgery (ERAS) program; as part of this program, every patient should be screened for malnutrition and given additional nutritional support if at risk. The main recommendations include pre-operative fluid and carbohydrate load, avoidance of fasting, and reintroduction of oral diet on the first postoperative day (5, 21).

Patients who are at moderate or high nutritional risk, particularly those undergoing surgery for upper GI cancer, should be considered for routine post-operative nutritional support (by oral or enteral route, as appropriate), and consideration should be given to continuing this support once the patient is discharged (22).

4.1. Upper GI cancer patients

ESPEN guidelines recommend oral/enteral immuno-nutrition (arginine, n-3 fatty acids, nucleotides) in upper GI cancer patients undergoing surgical resection (5). It was demonstrated that upper GI cancer patients experienced a reduction in post-operative infective complications when given oral/enteral "immune-modulating nutrition" in the peri-operative period. The term "immune-modulating nutrition" or "immuno-nutrition" refers to liquid nutritional supplements enriched with specific nutrients (arginine, n-3 fatty acids, nucleotides) (23).

Preoperative nutritional support is indicated for patients with dysphagia or significant weight loss during induction therapy. NCCN guidelines recommend a feeding jejunostomy tube since placement of a gastrostomy tube may compromise the integrity of gastric conduit for reconstruction (24). A percutaneous gastrostomy tube may be considered for patients with cervical esophageal tumors receiving definitive chemoradiation. Multidisciplinary expertise is recommended prior to placement of a feeding tube (24).

4.2. Radiotherapy

During radiotherapy, an adequate nutritional intake should be achieved by individualized nutritional counselling and/or with use of oral enteral nutrition (ONS) in order to prevent nutritional deterioration, maintain intake and avoid radiotherapy interruptions.

All patients undergoing radiation of the GI tract should receive a comprehensive nutritional assessment, adequate nutritional counselling and, if necessary, nutritional support according to symptoms and nutritional status. If nutritional support is required, this should be initiated early and if energy intake is inadequate, ONS are recommended (5).

In radiation-induced severe mucositis, ESPEN recommended enteral nutrition (EN) using nasogastric or percutaneous tubes (e.g. percutaneous endoscopic gastrostomies (PEG)). In patients with obstructing esophageal cancers and in settings with expected severe radiation-induced oral or esophageal mucositis, there is a high risk for weight loss, decreased physical performance, dehydration, decreased treatment tolerance and increased treatment interruptions.

In high-risk situations (T4 tumor, female sex, or combined chemoradiotherapy), prophylactic EN (as opposed to enteral feeding initiated after the onset of dysphagia) may maintain nutritional status and prevent interruption of treatment. Several, mostly retrospective observational studies observed improved body weight and lower rates of rehospitalization and treatment interruptions for patients treated with early compared to later or no EN (25, 26). PEG compared to radiologically inserted gastrostomies (RIG) appear to be associated with a lower risk of peritonitis and mortality. PEG, in comparison with nasogastric tubes, show that body weight may be maintained similarly, risk of tube dislodgement is lower and quality of life is possibly better. Nasogastric tubes are associated with less dysphagia and earlier weaning after completion of radiotherapy (25). The risks of pneumonia and other infections are similar (5, 25).

5. Nutritional Support Strategies for Patients with Metastatic Gastroesophageal Cancer

Nutritional support is important in the palliative setting as well since malnutrition and sarcopenia can lead to decreased survival and deterioration of quality of life. According to ESPEN guidelines, nutritional therapy in the palliative setting is beneficial as long as the patient is at higher risk of an earlier death due to malnutrition rather than cancer (5, 27). In this setting, nutritional support should improve quality of life and control symptoms.

Although guidelines always recommend a gradual transition from the less invasive (dietary counselling and ONS) to the more invasive nutritional intervention (PN), a compromised gastrointestinal tract may lead to select PN as the initial intervention, often combined to oral food intake to meet nutritional requirements (28). PN is mandatory in cases of complete bowel obstruction to prevent death from starvation and dehydration and could potentially improve quality of life and prolong survival. Whenever possible, it is important to maintain even a minimum intake of nutrients per os (e.g., complex carbohydrates, liquids), with the aim to support the mucosal immune response (29, 30).

For most patients with advanced disease who have an estimated life span that is measured in weeks to months, guidelines recommend against the use of enteral or total parenteral nutritional support (5). The routine use of nutritional support in patients with advanced incurable cancer is associated with a higher risk of treatment-related complications, and no evidence of a survival benefit, although the quality of the evidence is low (2,3,109-113).

However, in highly selected patients (e.g.., high-grade bowel obstruction or malabsorption from advanced cancer) who might otherwise have a prognosis that is measured in several months or years, home parenteral nutritional support may be considered after extensive deliberation among the health care staff, the patient, and caregivers (5). Even under such circumstances, however, parenteral nutrition is the exception rather than the rule,

EN should be considered if the gastrointestinal tract is functional, in the case of a life expectancy of several weeks or months. Endoscopic or surgical jejunostomy may be an option in the case of gastric obstruction/ dysmotility, whereas a nasogastric tube or a nasojejunal tube could be considered when short-term EN is expected (usually up to 6 weeks) and/or survival is uncertain (31, 32). When EN is unfeasible or refused by the patients, according to ESPEN 2009 and 2020 guidelines (33, 34) , PN should be considered for patients with life expectancy between 1 and 3 months.

6. Conclusions

Nutritional support is an essential component of management in upper gastrointestinal cancer, however there is limited knowledge of current clinical practice. Each patient should undergo the screening for assessment of nutritional status and should be treated following his specific needs according to the nutritional support algorithm and ESPEN guidelines. Timely nutritional support may positively impact the nutritional parameters and nutritional status of the patient, the quality of life, and tolerance to therapies.

Abbreviations

BIA – bioimpedance analysis
BMI – body mass index
CPN – central parenteral nutrition
CRP – C-reactive protein
DA – dietetic advice
DEXA – dual X-ray absorptiometry
EN – enteral nutrition
ERAS – enhanced recovery after surgery
ESPEN – European Society for Clinical Nutrition and Metabolism
GERD – gastro esophageal reflux disease.
GI – gastrointestinal
MNA – mini nutritional assessment
MST – malnutrition screening tool
MUST – malnutrition universal screening tool
NCCN – National Comprehensive Cancer Network
NRS – Nutritional Risk Screening
ONS – oral enteral nutrition
PEG – percutaneous endoscopic gastrostomy
PPN – peripheral parenteral nutrition
PN – parenteral nutrition
RIG – radiologically inserted gastrostomy
SGA-PG – patient-generated subjective global rating
QoL – quality of life
WHO – World Health Organization

Statements:

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The ABCs of Aneurysmal Bone Cysts: Is there a Role for Radiation Therapy?

Jose Ma. H. Zaldarriaga[1], Kenneth C. Sy[1], Angela Peña-Camacho[1]

[1] *Department of Radiation Oncology, St. Luke's Medical Center, Republic of the Philippines*

Corresponding author: Jose Ma. H. Zaldarriaga; **e-mail**: jmaphzaldarriaga@stlukes.com.ph

Abstract

Aneurysmal bone cyst (ABC) is a rare osteolytic lesion which, though benign, can have devastating effects on the patient's function and cosmesis. Surgery is the mainstay of treatment; however, for incompletely resected, inoperable, or recurrent ABCs, radiation therapy has been posited to be a feasible therapeutic modality. However, evidence on the possible role of radiation therapy in the management of ABCs remains in its infancy. This short review discusses what is currently known about the pathophysiology, natural history, epidemiology, and clinical presentation of ABCs. This will ultimately lead to a survey of the present literature on radiation therapy as used for ABCs.

Keywords: *aneurysmal bone cyst, radiation therapy, oncology*

Review Articles

1. Introduction

Aneurysmal bone cyst (ABC) is a benign, expanding, osteolytic lesion comprised of varisized blood-filled spaces separated by connective tissue septae containing trabeculae, osteoid tissue, and osteoclast-like giant cells (1-4). This distinct clinical entity derived its name from its initial description by Jaffe and Lichtenstein in 1942. They named these "peculiar blood-containing cysts of large size" as "aneurysmal bone cysts"- using "aneurysmal" to emphasize the "blown-out", distended contour of the affected bone; and "bone cyst" to describe how the lesion appears as a blood-filled cavity when entered through a thin shell of bone (5-6). This is now known to be a misnomer, as ABCs are neither true vascular aneurysms, nor true cysts.

2. Pathophysiology

The exact nature nor pathophysiology of the ABC, to date, remain elusive. Dabska and Buraczewski in 1969 were the first to describe its natural history, which they divided into four phases. The *initial phase* entails osteolysis of the marginal part of the bone with the elevation of the periosteum. The *growth phase* involves progressive destruction of bone. This is then followed by the *stabilization phase* which gives rise to the classic appearance of ABC as an expansile lesion with a distinct bony shell and

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osseous septations. Finally, the *healing phase* gives rise to progressive ossification of the lesion, thus giving rise to an irregular, bony mass (7).

Historically, Lichtenstein posited that the ABC is not a true neoplasm but, rather, a reactive lesion wherein the vascular disturbances in bone lead to increased intraosseous pressure, which subsequently causes local destruction and distention of the bone (6). This is supported by the findings of a later study by Camapanacci et al. which proposed that ABCs are secondary to an initial insult which in turn produces intraosseous bleeding which, subsequently, leads to the formation of a cyst. The cyst walls may contain capillaries that hemorrhage into the cavity, producing osteolytic and fibrotic tissue that would ultimately explain the lesion's characteristic histopathology (8).

Many cases of ABC, however, are without history of any- at least recalled- trauma. Indeed, emerging evidence has seen genetics to be implicated in the pathogenesis of ABC, furthering the hypothesis that, rather than being a reactive lesion, it is in fact a true neoplasm. In a histopathologic study, Oliveira et al. found that 69% of primary ABCs (i.e., ABCs not associated with a preexisting bone lesion) were associated with translocations in chromosomes 16 and 17 causing the juxtaposition of CDH11 and USP6. No such translocations were observed in secondary ABCs (9). Given these findings, up to 70% of ABCs are considered primary lesions, and 30% believed to be secondary to a different primary tumor which triggered the initial vascular insult (10).

3. Epidemiology and Presentation

ABCs are rare, with incidence rates ranging from 1.4 to 3.2 per million individuals (9,11-12). These lesions have been reported from ages ranging from 1 to 59 years old; however, up to 80% occur in patients less than 20 years of age (13). Males are slightly more often affected than females, with ratios up to 1.8:1.0. (11-12). Majority of ABCs- 50 to 60%- arise in the metaphysis of long bones, particularly the tibia and fibula. The second most common location is in the bony spine and sacrum.

The most common presenting symptoms of ABCs are pain, soft-tissue swelling, and/or a palpable expansile mass. (15). Because ABC is a benign disease, systemic symptoms such as fever, weight loss, malaise, nausea, and/or vomiting are uncommon (16).

On computed tomography (CT) imaging, ABCs appear as well-demarcated, multi-loculated, expansile, osteolytic lesions. MRI delineates these features more exquisitely, in addition to the internal septations as well as the lesion margin. ABCs are heterogeneously enhancing with a surrounding rim of low T1 signal. (1,13,16-17).

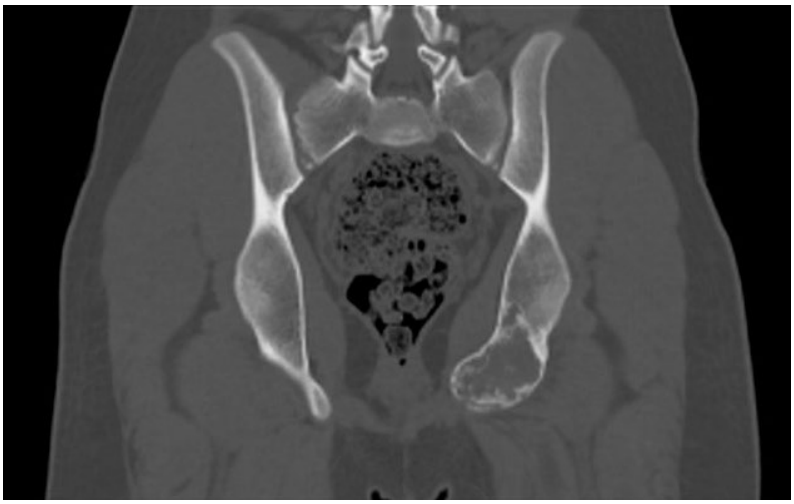

Figure 1. CT scan of an 8-year-old male with aneurysmal bone cyst of the left ischium. Coronal view shows a large, expansile, lucent bone lesion in the left inferior pubic ramus and ischium with internal septations. Margins are well-defined and measures approximately 4.5 x 2.9 x 8.3 cm. Image courtesy of Dr. David Cuete. https://radiopaedia.org/cases/aneurysmal-bone-cyst-of-ischium?lang=us

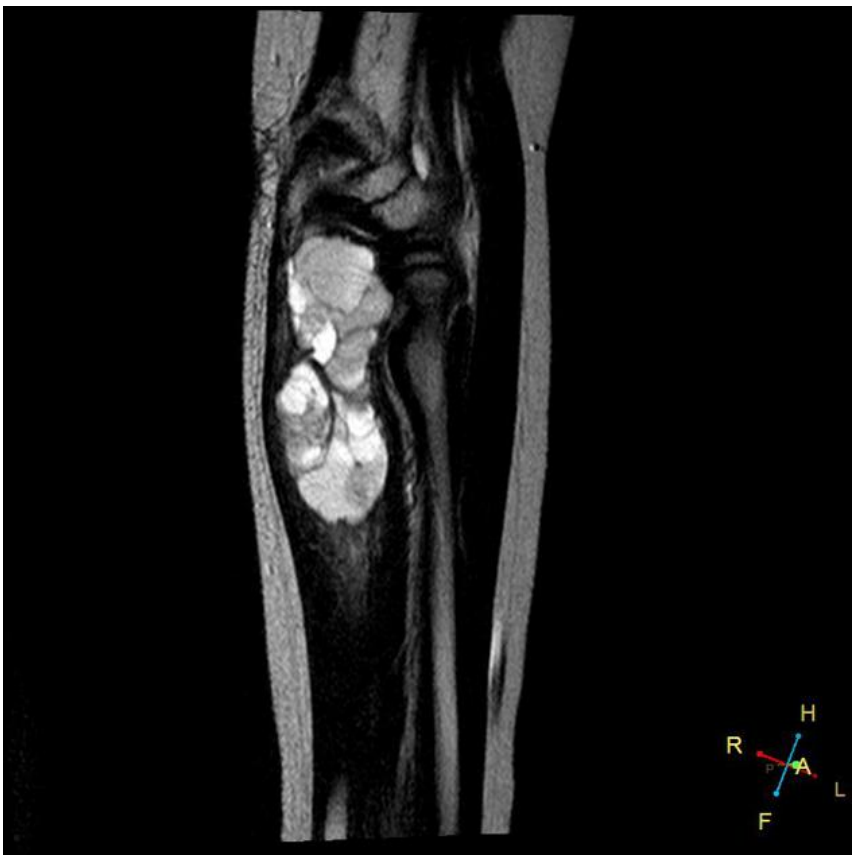

Figure 2. MRI of a 10-year-old female with aneurysmal bone cyst of the left proximal ulna. Sagittal T2-weighted image shows an expansile lesion in the proximal ulnar metadiaphysis with extension to the epiphysis. The lesion displays multiple cysts with fluid/fluid leveling. Image courtesy of Dr. Ahmed Abdrabou. https://radiopaedia.org/cases/aneurysmal-bone-cyst-8?lang=us

4. Treatment Modalities: Old and New

The preferred treatment modality for ABCs is surgery via intralesional curettage and bone grafting. The performed curettage can range from either the creation of a small fenestration to a large cortical window in the cyst to complete saucerization (16). A retrospective review by Gibbs et al. (1999) of ABCs of the extremities found that 4 of 34 ABC patients (12%) who underwent simple curettage had a local recurrence, whereas no patient who underwent complete cyst excision had a recurrence. (24).

Emerging minimally invasive treatment approaches include cryotherapy, sclerotherapy, and arterial embolization. Cryotherapy- the localized application of low temperatures to ablate or destroy the tissue in question- has been found to reduce the recurrence rate of ABCs. Peeters et al. (2009) reviewed 80 cases of ABCs located in various sites treated with cryotherapy and, at an average follow-up of 55 months, found an overall local recurrence rate of only 5% (25). Similarly, a single-institution review by Schreuder et al. (1997) found, among 27 ABC patients, a local recurrence rate of only 3.7% (26).

Sclerotherapy capitalizes on the theory that ABCs arise as vascular malformations. A retrospective review by Rastogi et al. (2006) of 72 patients with ABC treated with percutaneous sclerotherapy with polidocanol found a clinical response rate of 84.5% (27). In a similar vein, Varshney et al. (2010) reviewed 94 ABC patients treated either with curettage and bone grafting or sclerotherapy. With an average follow-up of 4.4 years, patients treated with curettage and bone grafting had an 84.8% healing rate compared to 93.3% among those treated with sclerotherapy. Recurrence rates were the same; however, the sclerotherapy group reported better functional outcomes with fewer complications (28).

Selective arterial embolization is likewise emerging as an alternative and novel therapeutic modality. A retrospective review by Rossi et al. (2010) of 36 patients with ABCs treated with arterial embolization noted complete clinical and radiologic response in 94% of patients. However, of these, 14 required more than one session of embolization. Furthermore, two cases of skin necrosis- one necessitating flap coverage- were reported (29).

5. The Role of Radiation Therapy: Emerging Evidence and Unanswered Questions

The role of radiation therapy (RT) in the management of ABCs is less well-defined and still emerging. RT has been used either in the definitive (as an alternative to surgery) or adjuvant setting for recurrent, aggressive, medically inoperable, or unresectable cases. A retrospective review was conducted by Zhu, Hitchcock, and Mendenhall (2015) of 12 patients with ABC who received curative-intent RT with or without prior surgical interventions at the University of Florida from February 1964 to June 2011. Eight (66.7%) of these patients were treated with definitive RT alone without prior surgeries and/or chemotherapy.

The total prescribed doses ranged from 20 to 60 Gy (median of 30.15 Gy) delivered via a variety of beam energies including 2-, 6-, 8-, 17-, 20-MV photons; and Cobalt-60. Interestingly, intensity modulated radiation therapy (IMRT) was used only for one patient, reflecting the fact that this RT modality still was unavailable prior to the 1990s. All but one patient were treated once per day, 5 days per week consecutively. 83.3% of patients received between 1.5 to 2.0 Gy per fraction. The radiation fields were targeted at the volume indicated by radiographs with a margin ranging from 1-3 cm.

With a follow-up duration spanning 3-36 years (median of 20.5 years)- to date the longest among studies exploring the role of RT in ABCs- RT was found to be well-tolerated in all 12 patients. 41.7% experienced only mild RT-related side effects: mild skin reaction in 16.7%, nausea and vomiting in 16.7%, and mild edema in 8.3%. All of such symptoms resolved upon completion of RT. Remarkably, pain relief was achieved for all patients 2-4 weeks upon completion of RT; 16.7%, in fact, even reported pain relief even before the RT course had concluded.

Resolution of the ABC cavity begins with gradual ossification of the soft tissue component. Post-RT radiographs revealed that the soft tissues inside the cystic cavity undergo ossification immediately after RT and may continue for up to 2 years post-RT. The ABC cavity in 16.7% of patients decreased to less than half of the original size; the sizes remained stable for the rest of the patients. This retrospective review, therefore, reported a 100% local control rate for RT, used either alone as definitive treatment or adjuvantly (18).

The outcomes reported in Zhu, Hitchcock, and Mendenhall's retrospective review are consistent with those of other older studies and case series. Bisecker et al. (1970) reported 4 cases of ABC treated with RT alone and 7 cases treated with RT for post-curettage recurrence. The reported 4-year local control rate from RT was 90.9% compared with 55% for surgery (19).

Marcove et al. (1995) reported a case series of 11 ABCs treated with primary RT alone. A local control rate of 90.9% was reported for RT and only 63.2% for surgery. However, one patient developed radiation-induced sarcoma. (20). A later case series by Boriani et al. (2001) explored 18 patients treated with RT, either alone or post-surgery) found a 0% rate of recurrence after at least 2 years of follow-up. However, 9 incidences of bony deformity were noted.

Indeed, the surveyed literature shows that RT offered outcomes that were just as good as, if not better than, surgery. Despite these promising data, however, there remains hesitation in using RT for ABCs, most especially for the pediatric population among whom majority of ABCs arise, because of the aforementioned isolated cases of chronic late effects and second malignancies. Retrospective series of pediatric patients treated with older radiotherapy machines and modalities two to three decades prior report a cumulative incidence of secondary radiation-induced malignancies ranging from 9.3 to 19% at 30 years post-radiation (30-32). However, Feigenberg et al. (2001) and Marks et al. (1976) assert that such incidences are likely due to the suboptimal radiation treatment received by these patients,

precluded by the now-obsolete radiation equipment and techniques reported in these studies. (21-22)

5. Conclusion

The potential role of radiation therapy for aneurysmal bone cysts (ABCs) - whether in the definitive or adjuvant setting- remains an active area of research. To date, there remains a dearth of literature on ABCs treated with radiation; what little data is available is largely derived from case reports and series. Nonetheless, this data is promising- revealing satisfactory local control rates with acceptable toxicities for ABCs treated with radiation. This is despite the fact that these reports were largely crafted in the pre-IMRT era. Since then, the field of Radiation Oncology has expanded exponentially. Radiation doses have become more conformal, treatment delivery has become more precise and reproducible, and knowledge of normal tissue constraints and toxicities has become more refined. Hence, more data in the present era- even in the form of case reports or series- would doubtless shed more light and define the yet-emerging role of radiation therapy in the treatment of ABCs.

Abbreviations:
ABC – Aneurysmal bone cyst
CT – Computed tomography
Gy – Gray
IMRT – Intensity-modulated radiation therapy
MRI – Magnetic resonance imaging
MV – Megavoltage
RT – Radiation therapy

Statements:
Author's contributions: JHZ, KSY, and APC conceived of the discussed topic; JHZ drafted the initial paper; KSY and APC made the final revisions to the final paper.
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Clinical Outcomes, Treatment and Testing Patterns in Patients with Advanced Non-Small Lung Cell Cancer with Epidermal Growth Factor Receptor Mutations: results of the Romanian Cohort From a Multi-national Retrospective Chart Review (REFLECT)

Mircea Dediu[1], Aurelia Alexandru[2], Cristina Ligia Cebotaru[3], Petra Curescu[4], Polixenia Iorga[5], Bogdan Gafton[6], Mihai Marinca[6], Amedeia Nita[7], Mihaela Pașca Fenești[8], Adrian Udrea[9], Roxana Lupu[10], Gabriela Teodorescu[10], Tudor E. Ciuleanu[3]

[1] *Sanador Oncology Center, Bucharest, Romania;*
[2] *Oncology Institute "Prof. Dr. Alexandru Trestioreanu" Bucharest, Romania;*
[3] *Oncology Institute "Prof. Dr. Ion Chiricuță" Cluj-Napoca, Romania;*
[4] *City Hospital Timișoara, Romania;*
[5] *University Emergency Hospital Bucharest, Romania;*
[6] *Regional Institute of Oncology Iași, Romania;*
[7] *City Hospital Ploiești, Romania;*
[8] *Oncohelp Medical Center Timișoara, Romania;*
[9] *Medisprof Cancer Center Cluj-Napoca, Romania;*
[10] *AstraZeneca Pharma, Bucharest, Romania*

Corresponding author: Mircea Dediu; **e-mail**: dr.mdediu@gmail.com

Original Reseach

Abstract

Background: REFLECT was a retrospective, non-interventional study conducted in eight countries, including eleven sites from Romania, on patients with advanced stage non-small cell carcinoma (NSCLC).

***Aim*:** To characterize clinical outcomes, treatments and the proportion of *T790M* EGFR mutation testing in patients with advanced non-small cell lung cancer (NSCLC) receiving first- or second-generation (1G/2G) epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) as first-line (1L) treatment in the Romanian cohort of an international study.

Methods: Comprehensive data were retrieved from the medical records of ninety patients with EGFR-mutated advanced NSCLC treated with 1G/2G EGFR TKIs between January 2015 and June 2018. All analyses are descriptive.

Results: The median age at lung cancer diagnosis in the Romanian cohort was 67.5 years, with 68% females. The distribution of EGFR TKIs was 50% erlotinib, 31% afatinib, and 19% gefitinib. First line treatment was stopped in 76 (84%) patients due to progression (79%), toxicities (3%), the patient's decision (1%) or surgery (1%). The median progression- free survival on 1L treatment was 12.0 months (95% CI 10.3-15.6), and the median overall survival from the start of first line therapy was 26.4 months (95% CI 22.4-34.2). EGFR *T790M* mutation

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testing was performed on 69% of patients at the time of progression on 1L therapy, with 57% of patients testing positive. Second-line (2L) therapy was started in 63% of patients discontinuing 1L therapy. Third-line treatment was started in 50% of patients discontinuing 2L treatment.

Conclusion: Survival results mirrored those of randomized trials. The suboptimal *T790M* testing rate (69%) underlines the importance of reflex testing procedures, while attrition rates on 1L (26%) emphasize the need for an upfront selection of the most effective treatments.

Keywords: *attrition rate, EGFR TKI, T790M testing, lung cancer, real-world data*

Clinicaltrials.gov registration number: NCT04031898
Date of registration on clinicaltrials.gov: 04-Jul-2019

1. Introduction

Lung cancer is a significant health concern; in 2020, in Romania, it ranked first as incidence (12.3% of all new cancer cases) and cancer-related mortality (19.8% of all cancer deaths) (1). The non-small cell lung carcinoma (NSCLC) is the primary histological type of lung cancer (85%), whereas most patients with NSCLC are usually diagnosed with the disease in advanced / metastatic stage (2,3). During the last decade, the progress in molecular testing led to the identification of actionable oncogenic mutations that transformed the treatment of NSCLC and significantly improved patients' outcomes compared to chemotherapy (4,5). In about 12% of the Caucasian population with advanced / metastatic NSCLC the epidermal growth factor receptor (EGFR) mutations found on the tyrosine kinase domain (3,4). The *EGFR* tyrosine kinase inhibitors (TKIs) of first-generation (erlotinib, gefitinib) and second-generation (afatinib, dacomitinib) changed the treatment paradigm (6), and established a new standard front-line treatment of advanced EGFR-mutated (EGFRm) NSCLC (3,7,8). However, after an initial response to these first- or second-generation (1G/2G) EGFR TKIs, the tumor develops resistance that requires a different therapeutic strategy (6,7,9). In 50-60% of cases, the resistance to treatment with 1G/2G TKIs is mediated by the *T790M* mutation in the *EGFR* domain (3,10). The third-generation EGFR TKI osimertinib targets both *EGFR* sensitizing, and *EGFR T790M* acquired mutations and demonstrated significant overall survival benefit as first-line (1L) treatment compared to erlotinib or gefitinib (11), and is currently the preferred option of advanced EGFRm NSCLC (12).

In oncology, real-world studies play an essential role in informing clinicians and policy-makers about the clinical characteristics of patients treated in routine clinical practice and the effectiveness and safety profile of approved medicines, complementing thus the data derived from randomized trials (13,14). Several real-world evidence focused on 1G/2G TKIs use in EGFRm NSCLC across various geographies (15). A recent medical chart review entitled REFLECT ("**R**eal-world treatment patterns, clinical outcomes, and **E**G**F**R / T790M testing practices in EGFR-mutated advanced non–smal**L** c**E**ll lung **C**ancer patients receiving First-Line EGFR TKI **T**herapy"; clinicaltrials.gov ID: NCT04031898) described clinical outcomes, treatment patterns, *EGFR* / *T790M* testing practices and attrition rates in 896 patients receiving 1L 1G/2G EGFR TKIs in seven small- and medium-sized European countries, and Israel (16). This study showed that one-third of patients (33%) did not receive any other treatment after discontinuing 1L EGFR TKI. Only two-thirds (71%) of the patients progressing on 1L EGFR TKIs were tested for the presence of *T790M* resistance mutation.

The analysis of Romanian patients' data included in the REFLECT study aims to provide a better understanding of real-life clinical outcomes, type of treatments, and proportion of *T790M* testing in patients receiving 1L 1G/2G EGFR TKI therapy for their advanced EGFRm NSCLC in this country.

2. Methods

2.1. Study design

REFLECT was a retrospective, non-interventional chart review study conducted from May to December 2019 in 49 study sites from Europe and Israel (16), which included 11 (22%) sites from Romania. The results of the Romanian cohort are presented here.

The study was performed in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice, and local regulations for observational studies The Ethics Committees approved the study protocol and study conducted in all participating countries. In Romania, the National Bioethics Committee for Medicines and Medical Devices approved the protocol (3SNI/13.05.2019) with a waiver of informed consent.

2.2. Patients

Eligible patients were adults with confirmed locally advanced or metastatic EGFRm NSCLC, initiated on a 1G/2G EGFR TKI (afatinib, erlotinib or gefitinib) as 1L treatment between January 01, 2015 and June 30, 2018. At the time of data collection, patients could have been alive or deceased. Exclusion criteria included enrolment in an interventional clinical trial for an experimental treatment for EGFRm NSCLC, administration of any other systemic therapy for advanced disease before 1L EGFR TKI and missing/unknown critical study information such as dates of initial NSCLC diagnosis, progression to advanced disease, the start of 1L TKI therapy, death or last available follow-up.

Eligible patients were enrolled consecutively, in the chronological order of initiating the 1L treatment with a 1G/2G EGFR TKI.

2.3. Objectives and outcomes measures

The primary objectives were the proportion of patients with advanced EGFRm NSCLC progressing on 1L 1G/2G EGFR TKI, real-world progression free survival (rwPFS) time and, the proportion of patients receiving second-line (2L) treatment, and types of 2L therapies. Secondary objectives and measures included baseline patient characteristics, rates of *T790M* mutation testing in patients progressing on 1L therapy, treatment patterns, and attrition rates in subsequent lines, the proportion of patients receiving osimertinib (including the line), proportion and characteristics of patients with central nervous system (CNS) metastases and leptomeningeal disease (LMD) and overall survival (OS).

The real-world time to disease progression was measured from the start of 1L treatment until the first documented, progression that was defined as radiological progression, the beginning of a new therapy, clinical progression evaluated by the treating physician, or death. Treatment patterns were assessed from the 1L 1G/2G EGFR TKI start until the last available follow-up, or death.

2.4. Statistical methods

Considering this study's the exploratory and descriptive nature, no formal hypothesis was defined in REFLECT. All analyses are descriptive. Results were summarized using means, medians, standard deviations (SD), and ranges for continuous variables and frequencies for categorical variables. The median rwPFS and OS with 95% confidence intervals (CI) were calculated with Kaplan-Meier methods.

3. Results

3.1. Study sites characteristics

The Romanian study sites included 6 (55%) regional or national cancer centers, 2 (18%) teaching university hospitals, 2 (18%) private hospitals, and 1 (9%) non-teaching hospital. Only three (27%) study sites provided in-house genetic testing services, with *EGFR* mutation tested reflex in almost half of participating centers (**Table 1**).

3.2. Patient characteristics

In total, Romanian investigators collected data from the medical records of 90 eligible patients. The median age at the time of diagnosis of the advanced NSCLC was 67.5 (range 34-86) years with 68% of patients being females. In all but two cases, the histological type was adenocarcinoma, and most patients (87%) had initial metastatic stage at diagnosis (**Table 2**). The median follow-up time was 19.8 (range 3.1-46.9) months.

The *EGFR* mutation status was determined from tissue biopsy (94%), liquid biopsy (4%) or cytology specimen (1%).

Table 1. Genetic testing characteristics in participating study sites

Characteristic	N=11 n (%)
In-house genetic testing	
Yes	3 (27)
No, with patients being referred to:	8 (73)
Central (regional/national) genetic laboratory	1 (9)
Affiliated genetic laboratory	1 (9)
Private genetic laboratory	6 (55)
Reflex *EGFR* mutation testing (at the time of advanced / metastatic stage diagnosis)	5 (46)
Reflex *T790M* mutation testing	4 (36)

Abbreviations: 1L=first-line; EGFR=Epidermal Growth Factor Receptor; TKI=tyrosine kinase inhibitor

Table 2. Clinical characteristics at the time of initial NSCLC diagnosis

Characteristic	All patients N=90
Age, median (range), years	67.5 (34-86)
Sex: female / male, n (%)	61 (68) / 29 (32)
Smoking status	
Current smoker	4 (4)
Former smoker	18 (20)
Never smoker	49 (54)
Unknown	19 (21)
Histology	
Adenocarcinoma	88 (98)
Mixed histology	1 (1)
Squamous cell carcinoma	1 (1)
Stage	
Early stage (IA, IB, IIA, IIB)	6 (7)
Limited regional (IIIA)	2 (2)
Locally advanced (IIIB)	3 (3)
Metastatic (IV)	78 (87)
Unknown	1 (1)
ECOG performance status	
0	13 (14)
1	51 (57)
2	15 (17)
3	2 (2)
Unknown	9 (10)
Site of distant metastases*	
Adrenal	10 (11)
Bone	26 (29)
Brain	17 (19)
Liver	17 (19)
Lung	51 (57)
Lymph nodes	20 (22)
Pleura	33 (37)
Other**	4 (4)
EGFR mutations	
Exon 19 deletion	44 (49)
L858R	31 (34)
Uncommon *EGFR* mutations	15 (17)

*Pooled data. Some patients presented multiple metastatic sites at the time of initial diagnosis of NSCLC.
**Other sites of distant metastases included: spleen (2 patients), pericardium (1 patient) and peritoneum (1 patient).
Abbreviations: ECOG=Eastern Cooperative Oncology Group, EGFR=Epidermal Growth Factor Receptor, NSCLC=non-small cell lung cancer

3.3. 1L EGFR TKI therapy characteristics

The distribution of 1L 1G/2G EGFR TKI therapies was erlotinib 50%, afatinib 31% and gefitinib 19%. Most 1L treatments were administered in monotherapy (92%). At the time of data extraction, 76 (84%) patients discontinued the 1L EGFR TKI therapy due to per-protocol progression events (n=71 (79%)), toxicities (n=3 (3%)), patient's decision (n=1 (1%)) and surgery (n=1 (1%)) (**Figure. 1**). All five (6%) patients discontinuing 1L EGFR TKI without documented progression did not start any other treatment line. First-line treatment was continued by 14 (16%) patients.

Relative to the entire cohort, the 1L progression events included radiological progression in 51 (57%) patients, clinical progression in 11 (12%) patients, death in eight (9%) cases and start of a new line of treatment without documented progression for one (1%) patient.

Median rwPFS was 12.0 (95% CI 10.3-15.6) months (**Figure. 2A**), with estimated 12-, 24-, and 36-month event-free probabilities of 50%, 21%, and 7%, respectively. Median OS was 26.4 (95% CI 22.4-34.2) months (**Figure. 2B**), with estimated 12-, 24, and 36-month probabilities of survival of 80%, 58%, and 35%, respectively.

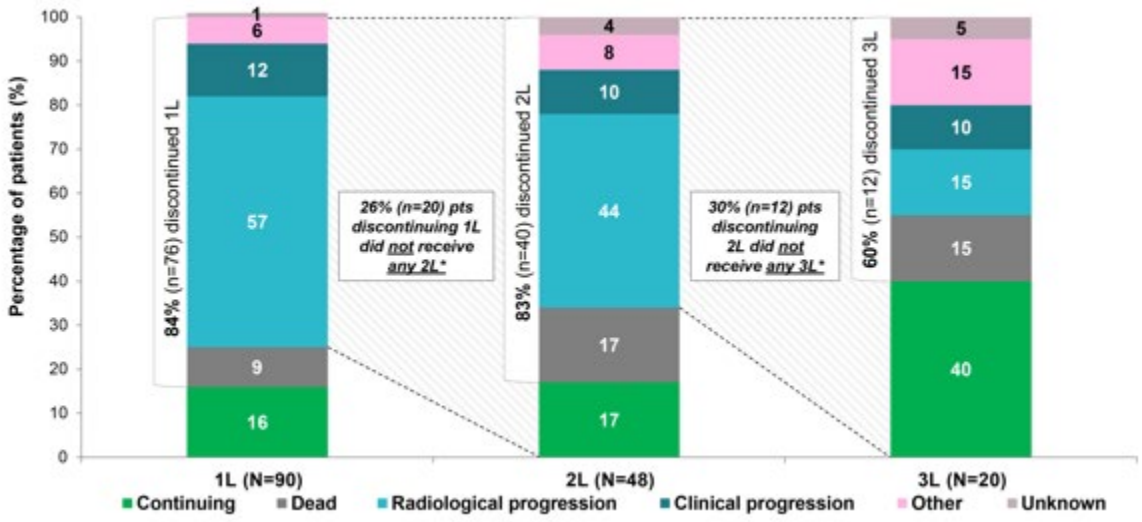


Figure 1. Reasons to discontinue 1L EGFR TKI, 2L and 3L in the Romanian cohort

**The count excludes deceased patients in each line. Due to rounding, percentages may not always be 100%.*
Note: The patient discontinuing 1L from unknown reasons started a new therapy line without documented progression, which is considered a per-protocol event.

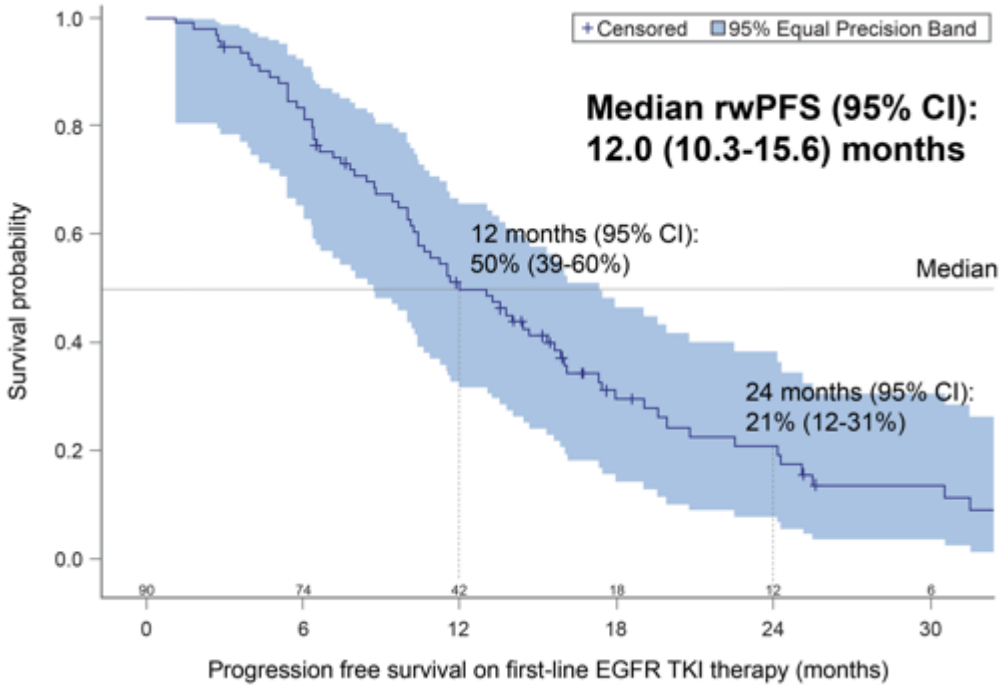
3.4. Second line treatment patterns and attrition rates

Of the 76 patients who discontinued 1L EGFR TKI therapy (**Figure 1**), 48 (63%) started second-line (2L) treatment and 28 (37%) did not receive any further treatment. Excluding patients deceased on 1L treatment (n=8, 11%), a total of 20 (26%) patients discontinuing 1L did not receive any subsequent treatment. The 2L treatment included osimertinib (52%), chemotherapy (46%), and targeted therapy afatinib (2%). At the time of data collection, 8 (17%) patients continued 2L.

3.5. T790M testing and osimertinib treatment

Of the 71 patients progressing on 1L EGFR TKI, the *T790M* mutation testing was reported for 49 (69%) patients, yielding positive results in 28 (57%) cases (31% from the enrolled population). The *T790M* testing was performed via liquid biopsy (67%), tissue biopsy (25%) or cytology (6%) (unknown 2%), after a mean (SD) time of 13.8 (8.5) months since the start of 1L TKI therapy.

(A)



Note: Survival probability at 36 months (95% CI) was 7% (2-16%).

(B)

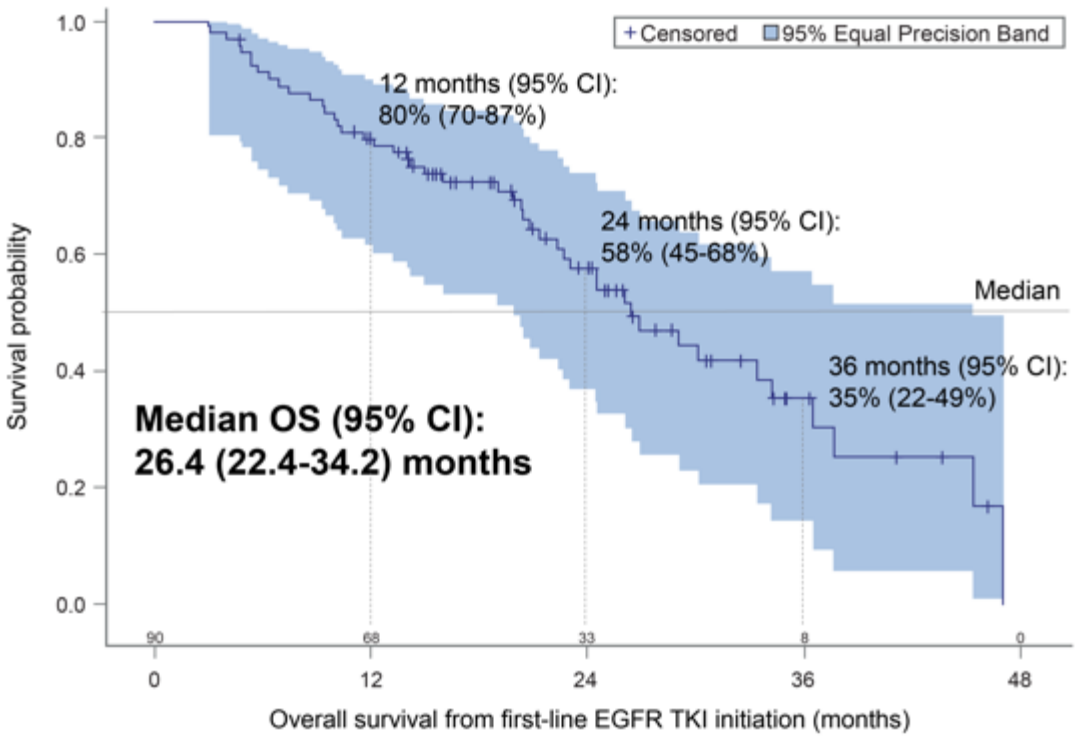


Figure 2. Survival outcomes on 1L 1G/2G EGFR TKI therapy:
(A) real-world progression free survival (rwPFS) and (B) overall survival (OS)

Of the 49 patients progressing on 1L EGFR TKI and tested for *T790M* mutation, 43 (88%) received 2L treatment with osimertinib (n=25 (58%)) or chemotherapy (n=18, 42%). All but one patient tested positive for *T790M* mutation received osimertinib post-progression (n=27 (96%)): most (n=25, 89%) as 2L treatment, 1 (4%) as 3L and 1 (4%) as 4L treatment. Of the 22 patients progressing on 1L EGFR TKI and not tested for *T790M* mutation, only 5 (23%) received 2L treatment with chemotherapy (n=4 (80%)) or targeted therapy (afatinib, n=1, 20%).

3.6. Third and subsequent lines treatment patterns

Of the 40 patients discontinuing 2L treatment (**Figure. 1**), half (n=20, 50%) started 3L. Excluding patients deceased on 2L treatment (n=8, 20%), a total of 12 (30%) patients discontinuing 2L did not receive subsequent treatments. The 3L treatments included chemotherapy (75%), immune therapy nivolumab (20%) and osimertinib (5%). At the time of data collection, 8 (40%) patients continued 3L.

Only 3 patients received 4L treatment: 2 chemotherapy and 1 osimertinib. Two patients died on 4L, and 1 patient started 5L with erlotinib, with radiological progression reported on 5L and no further treatment line.

3.7. CNS metastases and LMD

In total, CNS metastases were reported for 30 (33%) patients: for 19 (21%) patients the metastases were present at the start of the 1L EGFR TKI therapy. Eleven (12%) cases occurred during treatment after a median of 9.2 (range 3.6-23.7) months. The median age of all patients with CNS metastases was 67.5 (42-86) years, and 63% were females. The diagnosis of CNS metastases was made using computed tomography or magnetic resonance imaging scans in most cases (97%) and tissue biopsy in 1 case. Treatments recorded in 88% of patients with CNS metastases included whole brain radiation therapy (63%), stereotactic radiosurgery (13%), targeted therapy (13%), chemotherapy (7%) and surgical resection (3%); in 10% of cases no treatment and for 2% other (unspecified) were recorded. The median OS from the first brain lesion diagnosis was 25.6 (95% CI: 15.3-32.7) months in patients with CNS metastases at the start of 1L EGFR TKI treatment, and 5.4 (95% CI: 0.6-18.8) months in patients with CNS metastases developed during treatment.

LMD was reported for one patient after the start of the 1L EGFR TKI treatment. The LMD diagnosis was based on imaging scans, after a median of 20.1 months from the start of 1L EGFR TKI.

4. Discussion

To our knowledge, this is the first detailed analysis performed in Romania related to clinical outcomes, type of treatments, and *T790M* testing rates in patients with advanced EGFR mNSCLC receiving a 1G/2G EGFR TKI as 1L treatment during 2015-2018. The median rwPFS in our cohort was 12.0 (95% CI 10.3-15.6) months and median OS 26.4 (95% CI 22.4-34.2) months, similar to the rwPFS of 13.0 (95% CI 12.3-14.1) months and median OS of 26.2 (95% CI 23.6-28.4) months reported at the entire study level (16). Our findings are comparable to those reported in the registration trials of the 1G/2G EGFR TKIs (17,18). We found these results encouraging for a country from Central and South-Eastern Europe, regions with high mortality-to-incidence ratio (19) and still suboptimal access to innovative treatments (20).

In our cohort the 1L EGFR TKI distribution was erlotinib 50%, afatinib 31% and gefitinib 19%, whereas in the REFLECT primary study it was afatinib 45%, erlotinib 27% and gefitinib 27% (16), This result is in line with the reimbursement policy during 2015-2018, with erlotinib being the only EGFR TKI reimbursed until 2017, whereas the other two molecules were reimbursed afterwards (gefitinib the latest).

In the Romanian cohort, two-thirds (69%) of patients progressing on 1L EGFR TKI therapy underwent testing for the *T790M* resistance mutation, relatively similar to the rate of 71% reported in the primary REFLECT study (16). These figures are somehow lower compared with the testing rates of *T790M* of 70 – 90% communicated in other real-world European studies with a relatively similar design (21-25). The literature reports that *T790M* mutation is found at progression on 1G/2G EGFR TKIs in 50-60% of cases (3,10). Evaluating the results of our cohort, one may conclude that a higher

number of patients would have had a positive result if all patients would have been tested (estimated 36-43 patients vs actual 28), and consequently, a chance for receiving osimertinib in 2L. The REFLECT study did not collect the reasons for not performing the *T790M* testing, but a German study (23) reported fast deterioration of clinical status, severe comorbid conditions, and patient's decision as main causes for lack of *T790M* testing in progressive patients, which seem more related to the challenging tumor biopsy at progression. Guidelines recommend *T790M* testing upon the progression on EGFR TKI (3,8,12,26), and liquid biopsy is considered an acceptable method (12).

The suboptimal rate of *T790M* testing is one possible cause of the attrition rate observed in our cohort, where 31% of patients did not receive 2L treatment (among these, 9% deceased on 1L). A recent review showed that the attrition rate between 1L EGFR TKIs and 2L in EGFRm NSCLC is 36% in clinical trials, whereas in real-world studies it varies from 10% to 62% (27). Although in some cases an additional line of treatment may not translate in a clinical benefit, it is important to explore and address the local reasons of the attrition rates, and support the use the most efficacious therapy in 1L. Based on improved overall and CNS-specific efficacy and favourable toxicity profile demonstrated in the randomized clinical study FLAURA (11), osimertinib is now the preferred option for the 1L treatment of advanced EGFRm NSCLC (3,12,26). The first real-world studies also showed improved results with osimertinib in 1L. For example, in a retrospective analysis (28) including 172 patients with EGFRm NSCLC, the 12- and 18-month PFS was greater for osimertinib versus 1G/2G EGFR TKIs (80% and 70% vs. 64% and 39%, respectively, $p<0.0036$). The first prospective study exploring 1L osimertinib in 126 patients with advanced EGFRm NSCLC in real-life setting (29) showed median PFS of 18.9 months, median time to discontinuation 25.3 months and median OS not reached. While the long-term results of these real-world 1L osimertinib studies are awaited, the preliminary findings show better outcomes versus our cohort, where the 12- and 18-month PFS rates on 1L 1G/2G EGFR TKI were 50% and 21%, respectively, with a PFS of 12.0 months. t the time of this writing, reflex testing of *EGFR* mutations at diagnosis in Romania has significantly improved and is now aligned to updated guidelines, (3,12) and osimertinib is now reimbursed as 1L treatment.

The observational, retrospective nature of the REFLECT study, with a reduced number of inclusion and exclusion criteria is both a strength and a weakness: it provides an accurate snapshot of treatment and testing patterns at a specific timepoint, but it impedes the interpretation of results due to missing data and multiple confounding factors. In our analysis, a disadvantage was also the small sample size (n=90). A particular factor limiting the enrolment in Romania was the high number of patients with EGFRm NSCLC treated upfront with chemotherapy between 2015 and 2017, due to a delay of 1-3 months in the access to EGFR TKIs following the time lag in the Health Insurance Commission authorization. Nowadays, this drawback is solved, and the treatment authorization has become a rapid process, with access to targeted molecules provided as soon as the presence of the *EGFR* mutation is documented. However, the *EGFR* / *T790M* molecular testing is still not reimbursed.

5. Conclusions

This analysis is the first in Romania to provide detailed insights about clinical outcomes, type of treatments and *T790M* testing rate in EGFRm NSCLC patients treated in 1L with a 1G/2G EGFR TKI, before the standard of care in front-line setting changed to osimertinib. Survival outcomes in our cohort mirrored the data from randomized trials and other real-world studies. However, the *T790M* testing rate was suboptimal, with only 2 in 3 patients progressing on 1L EGFR TKI being tested for the resistance mutation. In addition, after 1L treatment, 1 in 3 patients did not receive any subsequent line. These findings emphasize the need for reflex testing at progression on 1L to ensure improved treatment strategies. In light of the current treatment landscape, our results stress the importance of upfront reflex testing to allow optimal outcomes through the selection of the most effective 1L treatments.

Abbreviations:
1G/2G – first- and second-generation
1L – first-line
2L – second-line
3L – third-line
CI – confidence interval
CNS – central nervous system
ECOG – Eastern Cooperative Oncology Group
EGFR – epidermal growth factor receptor
EGFR-m – EGFR-mutated
LMD – leptomeningeal disease
NSCLC – non-small cell lung cancer
OS – overall survival
rwPFS – real-world progression free survival
PFS – progression free survival
TKI(s) – tyrosine kinase inhibitor(s)
SD – standard deviation.

Statements:
Authors contributions: MD, AA, CLC, PC, PI, BG, MM, AN, MPF, AU, TEC have been involved in the acquisition and interpretation of data, critical revision of the article and approved the final version to be submitted. RL has been involved in the interpretation of data, critical revision of the article, supervision and approved the final version to be submitted. GT has been involved in the interpretation of data, critical revision of the article, and approved the final version to be submitted.
Consent for publication: As the corresponding author, I confirm that the manuscript has been read and approved for submission by all named authors.
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Neuroendocrine Carcinoma of the Prostate: A Case Report

Mădălina-Cristina Negulescu[1], Mihaela Mihai[2], Iulia Magdalena Gramaticu[1]

[1]*Department of Oncology, Fundeni Clinical Institute, Bucharest, Romania*
[2]*Department of Pathology, Fundeni Clinical Institute, Bucharest, Romania*

Corresponding author: Iulia Gramaticu; **e-mail**: iuliagramaticu@yahoo.com

Abstract

Poorly differentiated neuroendocrine carcinomas are rare. Most of them arise from the lung, and only 9% are found in extrapulmonary sites. In the prostate, neuroendocrine cells are more commonly present compared to other organs of the genitourinary tract.

We present the case of a 67-year-old male patient who was investigated for constipation, loss of appetite and pelvic-perineal pain; a large prostatic mass was discovered upon further investigation. After a thorough work-up and multidisciplinary approach, the patient was diagnosed with de novo small cell neuroendocrine carcinoma of the prostate with multiple metastases. He underwent five cycles of chemotherapy with cisplatin and etoposide before we evaluated the therapeutic response by CT scan, which showed partial response according to RECIST v 1.1. Due to significant nephrotoxicity, the treatment was discontinued after the 6th cycle and a follow-up after three months was recommended.

The rarity of this case made the diagnosis process challenging, but an accurate diagnosis was possible with the multidisciplinary team`s involvement. The treatment was initiated according to the international guidelines concerning extrapulmonary poorly differentiated neuroendocrine carcinomas/ large or small cell carcinomas. Although the evaluation showed partial response, small cell neuroendocrine carcinoma of the prostate is an aggressive tumor with a poor prognosis.

Keywords: *prostate cancer, neuroendocrine carcinoma, small cell neuroendocrine carcinoma, multidisciplinary team, case report*

Case Reports

1. Introduction

Neuroendocrine differentiation of prostate cancers has gained recent interest because of their relationship to castration resistant disease. The 2016 WHO classification of prostate cancers with neuroendocrine differentiation incorporates four different morphological subtypes, one of them being small cell neuroendocrine carcinoma (1). This particular subtype is rare; clinically it is characterized by an aggressive evolution and rapid spread. Herein, we present the case of a patient with de novo small cell neuroendocrine, poorly differentiated carcinoma, with multiple metastases.

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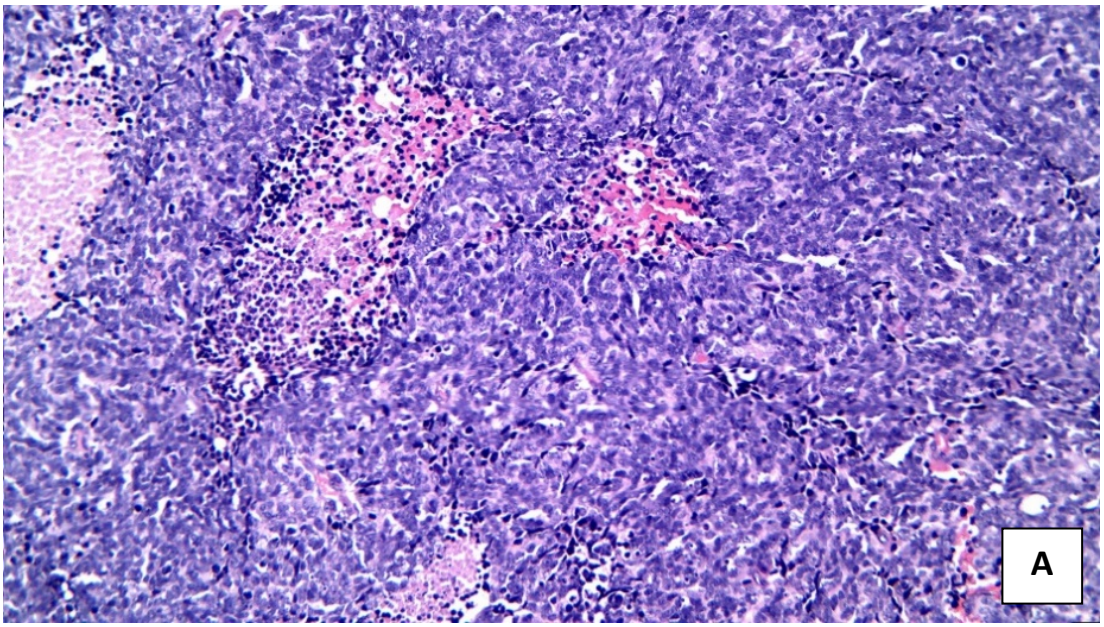
2. Case presentation

A 67-year-old male was investigated for constipation, loss of appetite and pelvic-perineal pain in August 2021. The patient had no significant family history, was only under treatment for arterial hypertension grade II, was a never-smoker and was an occasional alcohol consumer. The laboratory findings showed only an elevated creatinine level at the initial presentation. A colonoscopy was performed that did not show any evidence of a mass. The abdominal and pelvic CT scan revealed the prostate with irregular margins and 57/60/55 mm in size. A coralliform calculus was described in the left kidney and a renal scintigraphy showed a diminished renal function. The patient was admitted to the Urology Clinic in November 2021 where he underwent a series of investigations – urinary tract ultrasound, urethrocystoscopy and proctoscopy. The transrectal prostatic ultrasound revealed a large prostatic mass, which invaded the seminal vesicles bilaterally and compressed the anal canal. Several biopsies were performed. Moreover, *PSA*, *CEA* and *CA 19-9* values were elevated. A thoracic CT scan was performed and pulmonary metastases and several osteolytic lesions were also described.

At this point, the patient was referred to the Oncology department for constipation, fatigue and pain management. He was complaining of severe pain in the perineal area, which was insufficiently controlled with tramadol and paracetamol. The physical examination revealed pallor and mild pain on palpation in the hypogastric region. Mild anemia with iron deficiency and slight elevation of the creatinine level was also found. The treatment for pain management was initiated with fentanyl patches and anti-inflammatory medication. Additionally, prokinetics and laxatives were prescribed.

The histopathologic report of the prostatic biopsy revealed neuroendocrine morphology with small cells, foci of necrosis and high mitotic rate, suggestive of a poorly differentiated carcinoma with small cells (Fig. 1). Immunohistochemically, the tumor cells showed a high ki67 of 75-80%, NKX3.1 negative and TTF-1 positive (Fig. 2); the neuroendocrine markers (synaptophysin, CD56, chromogranin A) were intensely positive (Fig. 3). Therefore, the final diagnosis was poorly differentiated neuroendocrine carcinoma of the prostate stage IV with pulmonary and bone metastases.



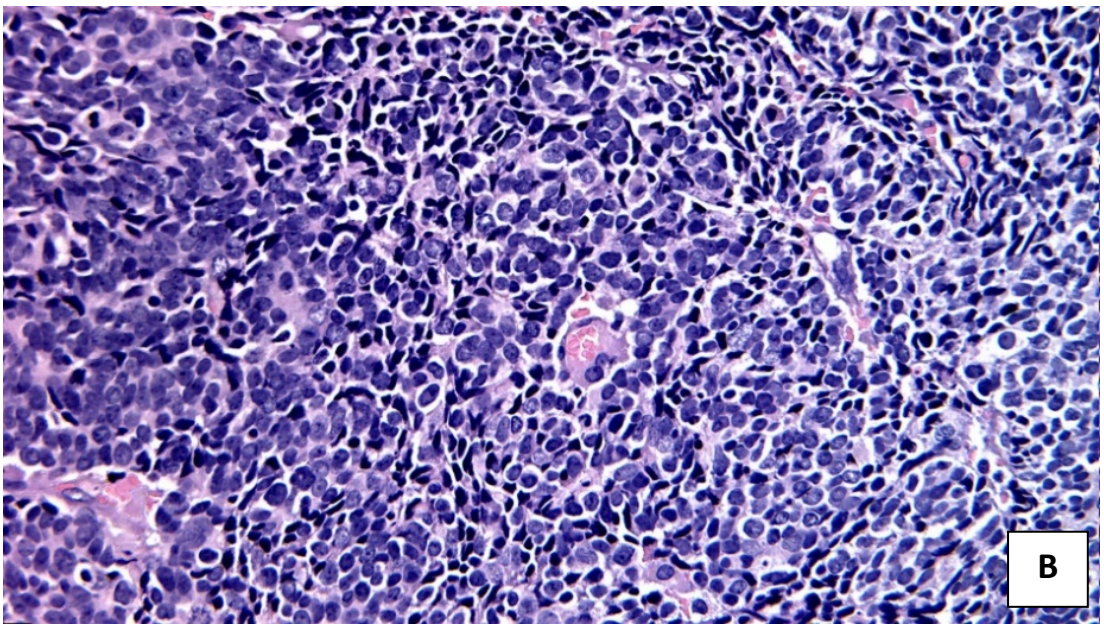


Figure 1. A: HE staining 20X; B: HE staining 40X
(Courtesy of Mihaela Mihai MD, Fundeni Clinical Institute)

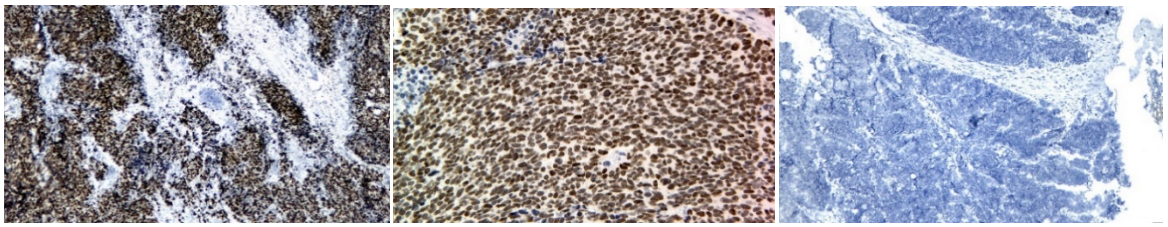
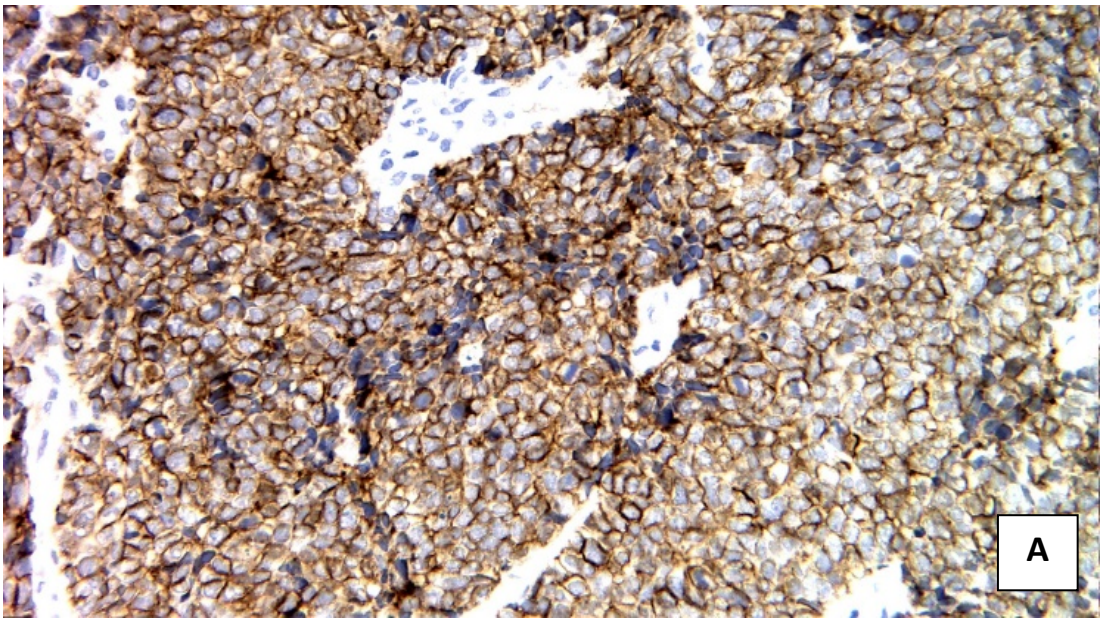


Figure 2. From left to right: Ki-67 10X – 75-80%, NKX3.1 10X - negative, TTF-1 40X positive;
(Courtesy of Mihaela Mihai MD, Fundeni Clinical Institute)



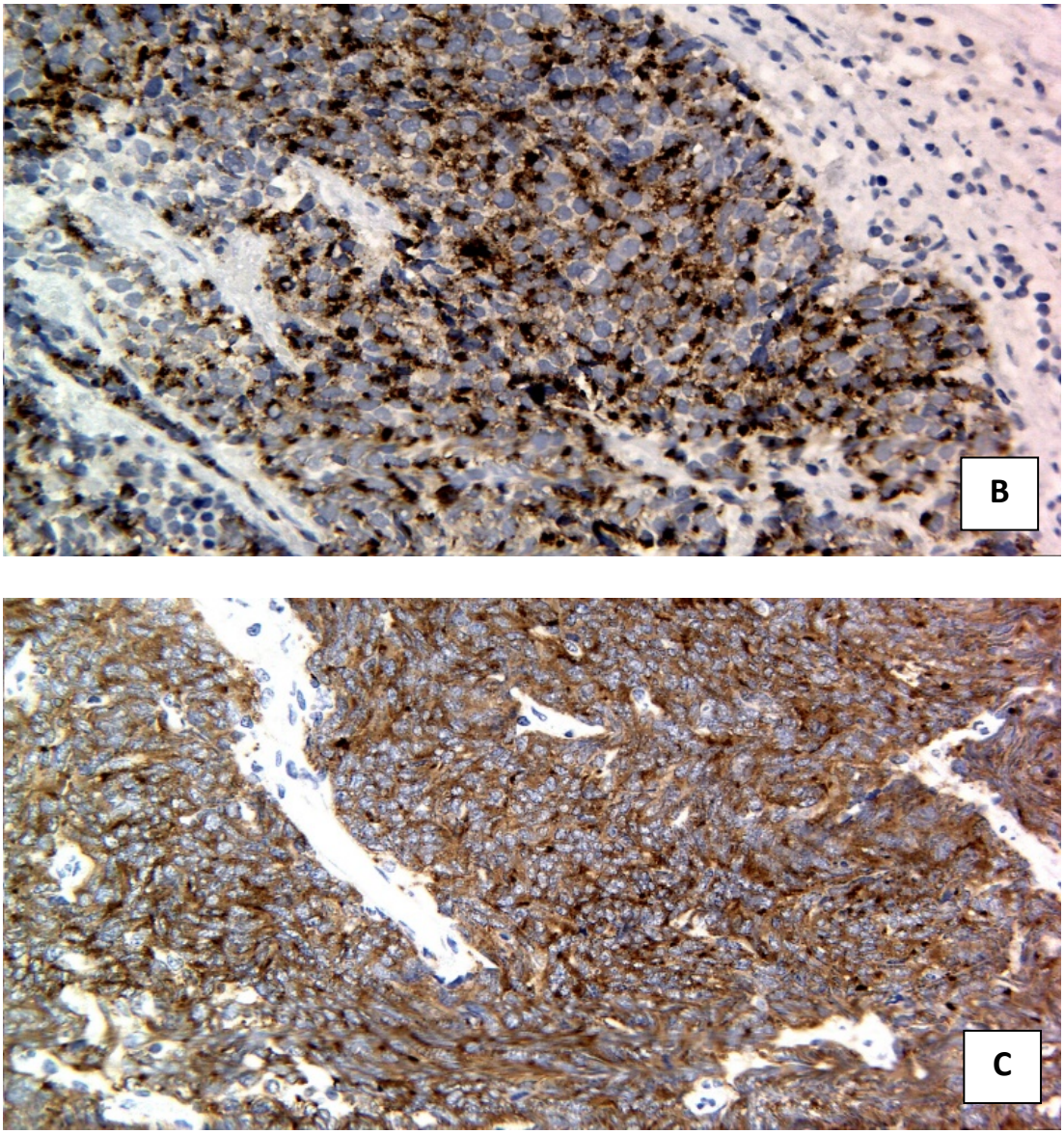


Figure 3. A: CD56 40X- positive; B: SYN 40X – positive; C: CG-A 40 X – positive. (Courtesy of Mihaela Mihai MD, Fundeni Clinical Institute)

The multidisciplinary team assessed the case of this patient and it decided on the prompt initiation of palliative chemotherapy. Accounting for the aggressive nature of the tumor, an abdominal and pelvic CT was repeated. Multiple bilateral liver metastases (the largest in the VI th segment with a maximum diameter of 68/47 mm) and a large celio-mesenteric lymphadenopathy were also described. At this point, the pelvic tumor measuring up to 10/9 cm invaded the posterior-inferior bladder wall and the anterior rectal wall and multiple pelvic lymph nodes (maximum diameter of 50/30 mm encompassing the left iliac vein) and osteolytic lesions were identified.

The patient started chemotherapy at the beginning of December 2021 with cisplatin 80 mg/ m2 on day one and etoposide 100 mg/m2 on days 1-3, every 21 days, planned for 4-6 cycles. The treatment was generally well tolerated. The adverse events were anemia (grade 1/ 2), asthenia (grade 1) and elevation of the creatinine level (grade 1/ 2). Cisplatin pre-and post-hydration protocols were followed to reduce nephrotoxicity. Still, at the end of the 6th chemotherapy cycle, the creatinine level

was 1.9 mg/dL and creatinine clearance was 32 mL/min. Thus, the administration of cisplatin was discontinued.

In March 2022, the patient was evaluated with a CT scan (thoracic, abdominal and pelvic) which revealed partial response according to RECIST v1.1.

There was no evidence of pulmonary metastases, or abnormal lymph nodes in the celio-mesenteric area. The hepatic lesions showed at least a 50% reduction in diameter compared to baseline (e.g. the lesion in segment VI was 25/15 mm versus 68/47 mm at baseline). The prostatic tumor had a maximum diameter of 58/56 mm versus 100/90 mm at baseline (Fig. 4).

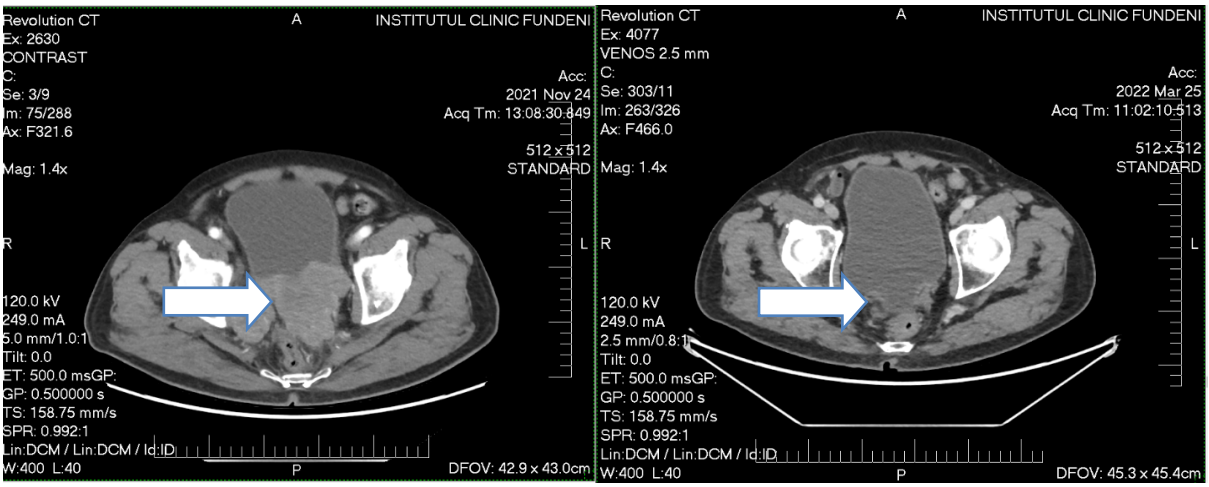


Figure 4. Prostatic tumor – on the left side in November 2021 (max. diameter 100/90 mm); on the right side in March 2022 (max. diameter 58/56 mm)

The patient was discharged in April 2022 with recommended follow-up after three months, and with symptomatic treatment.

After 3 months, the patient was evaluated with a CT scan of the thorax, abdomen and pelvis. The scan revealed stable disease according to RECIST v1.1. A month later, in august 2022, the patient was brought in for dizziness, confusion and headaches. An emergency CT was performed a few days prior, which described multiple brain metastases. He underwent whole brain palliative radiotherapy and palliative chemotherapy with Irinotecan, leucovorin and 5-fluorouracil (FOLFIRI) starting in September 2022.

3. Discussion

Large/small cell poorly differentiated neuroendocrine carcinomas are aggressive tumors with high mitotic rates and high Ki-67 index, which most of the time require combined treatment. Neuroendocrine carcinomas are rarely associated with carcinoid syndrome and are most of the time found as pulmonary masses – according to the SEER database, while only 9% of NECs are extrapulmonary (2). Of all cases of prostate cancer, only 0,5-2% are small cell carcinomas (3).

Two mechanisms are incriminated in the pathogenesis of neuroendocrine prostatic tumors. Most frequently, the neuroendocrine features appear as a result of an acinar adenocarcinoma undergoing transformation following long-term hormone therapy, with the loss of androgen receptors. The second mechanism involves the malignant transformation of the neuroendocrine cells usually present in the prostate (4). De novo small cell carcinoma of the prostate is a rare occurrence; in one single-center study conducted by Spiess et al, two-thirds of the patients included developed SCC after being diagnosed and treated previously for prostatic adenocarcinoma (5).

The 2016 WHO classification of prostatic cancers acknowledges four different types of prostatic cancers with neuroendocrine differentiation: adenocarcinoma with neuroendocrine differentiation, well-differentiated neuroendocrine tumor/carcinoid and large or small cell neuroendocrine carcinomas of the prostate (6). A small cell neuroendocrine carcinoma diagnosis can be made by microscopic examination of tumor morphology on H&E stain. The tumor cells show characteristic neuroendocrine morphology, with scant cytoplasm, hyperchromatic nuclei without conspicuous nucleoli, frequent mitosis, nuclear molding, rosette-like structures, and prominent necrosis. Immunohistochemically, these tumors are positive for at least one of the neuroendocrine markers - synaptophysin, chromogranin and CD56 (7, 8).

Several differential diagnoses were considered regarding the anatomic site of origin for this tumor. A pulmonary or pancreatic neuroendocrine carcinoma metastatic to the prostate were considered, as well as neuroendocrine differentiation of a primary prostatic adenocarcinoma. The immunohistochemical report excluded a diagnostic of prostatic adenocarcinoma because NKX3.1, a marker highly specific for prostatic adenocarcinoma, was negative. Regarding TTF-1 positivity, as seen in our patient, different studies highlighted the possibility of this occurrence in de novo small cell neuroendocrine carcinomas of the prostate, in over 50% of cases (9).

A literature review conducted by Palmgren et al reviewed articles published from 1983 until 2005 regarding small cell carcinomas of the prostate. Patients with small cell carcinoma of the prostate had different clinical presentations – voiding symptoms, neurologic and constitutional symptoms were among the most frequent (3). The case described by Bhandari et al presented with biochemical modifications of the PSA level, without any other clinical symptoms. Unfortunately, the disease quickly progressed and therapeutic interventions focused on symptom control and palliative care, highlighting once again the aggressive nature of this tumor (10).

Metastases were present in most of the patients in these studies at the time of diagnosis, with liver, lung and bone metastases being the most frequent. Most patients included in these studies had more than one metastatic site (3, 5, 11). Conteduca et al reported 82,8 % of patients with metastases at the time of neuroendocrine small cell carcinoma of the prostate diagnosis, all of which had liver metastases (12).

A population-based study conducted by Deorah et. al regarding the survival of patients diagnosed with small cell carcinoma of the prostate included 191 cases reported in the SEER database from 1973 until 2003. The one-year overall survival rate was 50,9%, with progressively lower rates at two and five years (27,5 and 14,3% respectively), with median survival being just 19 months (11).

Small cell carcinomas resemble other small cell primaries. Being such rare tumors, treatment paradigms are extrapolated from small cell lung cancer. Currently, systemic therapy regimens for the metastatic setting rely on cisplatin and etoposide, with carboplatin being a good replacement if needed. FOLFOX or FOLFIRI can also be used (2). Although remission has been reported in different studies after aggressive systemic therapy, these responses are short-lived. Some studies reported progression free survival at just six months in (5). The Impower133 study brought improvements in OS and PFS in small cell lung cancer with the PD-L1 inhibitor atezolizumab in combination with standard chemotherapy, becoming standard of care. Based on this, it was hypothesized that checkpoint inhibitors might offer a new therapeutic option in small cell carcinoma of the prostate. Wee et al identified patients that received chemotherapy+atezolizumab in the first-line setting of a metastatic prostatic small cell carcinoma. This study did not show any benefit from the addition of immunotherapy in this setting, with a median PFS of 3,4 months and OS of 8,4 months (median follow-up of 6,5 months) (13). On the other hand, a case report published in 2018 reported a sustained response with pembrolizumab in a 78-year old male with platinum-refractory metastatic small cell carcinoma of the prostate with a history of high-grade adenocarcinoma (14).

4. Conclusion

Small cell neuroendocrine carcinoma of the prostate is an infrequent entity, with a highly aggressive evolution. The histopathologic and

immunohistochemical diagnoses were challenging and highly disputed in this case.

A multidisciplinary approach involving a pathologist subspecialized in genitourinary pathology was necessary for the appropriate diagnosis and treatment strategy. Clinically, the patient had an improved performance status and a good response to platinum-based chemotherapy, as seen in other reported cases. These responses seem to be short-lived, and the overall prognosis of these patients is poor. The optimal management is not well defined, given that the clinical experience is scarce at this moment and there is a constant need of new data and new treatment options in order to improve the outcomes of these patients.

Abbreviations

CT – computed tomography
PSA – prostate specific antigen
CEA – carcinoembryonic antigen
CA19-9 – carbohydrate antigen 19-9
H&E – hematoxylin and eosin
SYN – synaptophysin
ChA – chromogranin A
NEC – neuroendocrine carcinoma
SCC – small cell carcinoma
SEER – the surveillance, epidemiology and end results program
PD-L1 – programmed death-ligand 1
OS – overall survival
PFS – progression free survival

Statements:

Authors' contributions: MN wrote the manuscript, IG & MM revised the text.

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

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Ethical Approval: The treatment strategy was approved by the institutional tumor board (Fundeni Clinical Institute, Bucharest, Romania).

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Second, Peculiar Recurrence of a Wilms Tumor- Pleural and Late

Andrada Țurcaș[1,2,3], Cristina Gheară[1,4], Vlad Gălățan[1], Cristina Blag[5], Dana Cernea[1]

[1] *Radiotherapy Department, Oncology Institute "Prof. Dr. Ion Chiricuță", Cluj-Napoca, Romania*
[2] *Oncology Department, University of Medicine and Pharmacy "Iuliu Hațieganu", Cluj-Napoca, Romania*
[3] *The European Society for Paediatric Oncology (SIOP Europe), Brussels, Belgium*
[4] *Faculty of Physics, Babeș-Bolyai University, Cluj-Napoca, Romania*
[5] *Clinical Emergency Hospital for Children – Pediatrics Clinic 2, Cluj-Napoca, Romania*

Corresponding author: Andrada Turcas; **e-mail**: andradaturcas@outlook.com

Abstract

Nephroblastoma (Wilms tumour) is the most common kidney malignancy in children and one of the most frequent abdominal tumours diagnosed in pediatric patients. We present the case of a 2-year-old boy diagnosed with intermediate-risk, regressive-type nephroblastoma of the left kidney in 2010. He was treated with neoadjuvant chemotherapy followed by surgery and chemotherapy (following the International Society of Pediatric Oncology- SIOP protocol). After 11 months a metastasis was discovered in the left lung and the patient was (re)classified as being high risk and treated with seven cycles of chemotherapy. After nine disease-free years, the routine follow-up chest CT scan showed a 10/5cm tumor in the left lung involving the pleura. The tumor was completely resected, and pathology confirmed a distal recurrence of nephroblastoma. The patient was further treated according to the UMBRELLA protocol (BB group) with chemotherapy and local irradiation. The tumor bed was irradiated with 25.2 Gy/14 fr, using Helical Tomotherapy. Following radiotherapy, he received a high dose chemotherapy and autollogus stem-cell transplant, with a good response and without disease recurrence.

Keywords: *pediatric oncology, radiotherapy, nephroblastoma, Wilms tumour, kidney tumour*

Case Reports

1. Introduction

Nephroblastoma (Wilms tumour) is the most common kidney malignancy in children and one of the most frequent abdominal tumours diagnosed in pediatric patients (1). It usually occurs in otherwise healthy individuals, but in about 10% of cases may occur in the context of genetic disorders such as WAGR (Wilms, Aniridia, Genitourinary anomalies, mental Retardation) syndrome/ 11p deletion or other Wilms Tumor 1 (WT1)- (1) related genetic syndromes (2). Nephroblastoma is usually diagnosed using imaging, both abdominal CT and MRI, and most of the time a biopsy is not required nor indicated (3, 4). In terms of treatment, the European recommend-dations (SIOP protocol) include induction chemotherapy followed by surgery, then by risk-adapted adjuvant therapy, defined as chemotherapy with or without radiotherapy to the affected abdominal flank (5, 6). A more

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recent approach regarding radiotherapy is carefully aiming towards a more conformal irradiation, using advanced techniques such as IMRT/VMAT and smaller target volumes, in order to reduce toxicities while keeping good local control (7). On the other hand, the Children Oncology Group (COG) approach is up-front surgical resection followed by systemic therapy and radiation. This approach offers the advantage of having an initial pathologic assessment, without any chemotherapy-induced histological changes, but it also increases the risk of a tumour spill (8).

Survival of Wilms tumour patients can reach up to 90% (9) and recurrences usually occur in 3-20% of the patients, but can reach as high as 50%, depending on several prognostic factors such as age at diagnosis, disease stage, histology, response to induction chemotherapy, and molecular factors such as LOI 11p15 or LOH 11p15 (10, 11).

2. Case Report

A two-year-old boy presented in 2010 in a county hospital with a mass located in the left abdominal flank, which was diagnosed as nephroblastoma based on abdominal imaging. He received induction chemotherapy, following the SIOP WT 2001 protocol: 4 cycles of AV (Actinomycin D 45 microgram/kg week 1,3 + Vincristine 1.5mg/square meter/week 1,2,3,4), followed by surgical resection of residual tumour. The pathology report confirmed the diagnosis of nephroblastoma, describing more than two thirds of the tumour showing chemotherapy-induced changes, without viable tumoral cells being present, consistent with intermediate risk, stage III, regressive type Wilms tumour. The pathology report emphasised the presence of macroscopic extracapsular tumor extension and chemotherapy induced tumour necrosis that encompassed almost the entire tumor volume. There was no vascular or lymphatic invasion, with only one of the resected lymph nodes showing signs of necrosis. The patient continued systemic AV chemotherapy for 27 weeks. Flank irradiation recommended by the SIOP protocol was not delivered.

Eleven months after the last chemotherapy cycle, the patient returned with a left lung solitary nodule, which was diagnosed as a lung metastasis by imaging. This patient had several adverse prognostic factors including being older than 2 years of age, and an advanced stage (III, intermediate risk) and having an early recurrence (under 1 year since first diagnosis). However, the initial tumour had favourable histology, thus the patient was re-classified as high risk (Group C at recurrence) and received 7 cycles of Cyclophosphamide 440mg/square meter, Carboplatin 500mg/square meter and Etoposide 100mg/square meter, following the United Kingdom Children's Cancer Study Group Wilms Tumour Group Protocol (UKWR 2001) protocol for relapsed Nephroblastoma.

After a nine-year disease-free interval, a routine follow-up chest CT scan (**Figure 1**) performed in February 2021 showed a left pleural-based lung nodule (10/5cm), compressing the left lung and invading into the left chest wall. It was considered a second, late recurrence of the Wilms tumor. The metastasis was completely resected, and pathology confirmed nephroblastoma. The pathology report described a tumour surrounded by a pseudo-capsule, with no anaplasia, vascular or lymphatic invasion, but presence of some blastemal tumour cells outside the pseudo-capsule. The resection margins were clear, but narrow (1 mm from the tumoral edge). Immunohistochemical stains for PAX8, CKAE1/AE3, CD56 and Vimentin (positive in stromal cells and diffusely positive in tumor cells) were positive. CD99, Desmin, Synaptophysin and WT1 stains were negative. Following surgery, the patient received 4 cycles of chemotherapy (Ifosfamide/ Cyclo-phosphamide, Carboplatin, Etoposide), as recommended by SIOP-UMBRELLA 2016 protocol for relapsed nephroblastoma, in this case in the left lung.

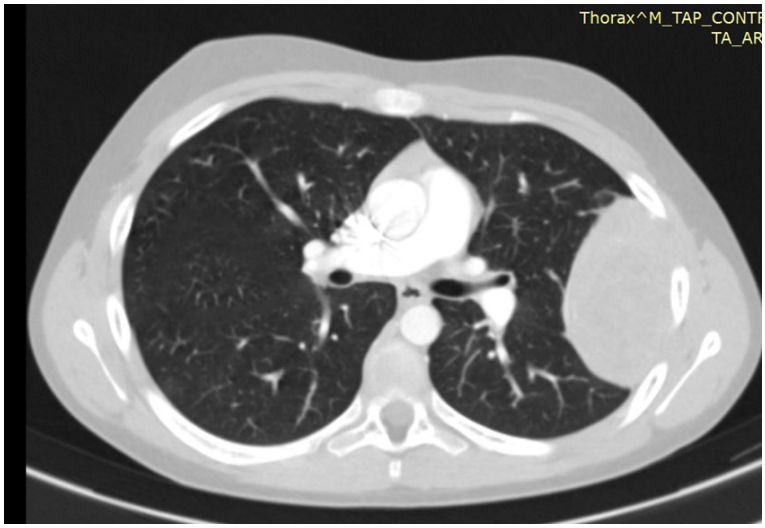

Figure 1. Chest CT Showing the Second Pleuro-Pulmonary Recurrence in the Left Lung

Table 1. Dosimetric Comparison for the PTV

	HT			VMAT			3DCRT		
	Dmax (Gy)	**$V_{95\%}$**	**CI**	**Dmax (Gy)**	**$V_{95\%}$**	**CI**	**Dmax (Gy)**	**$V_{95\%}$**	**CI**
PTV	28.43	99.5%	1.000	27.3	99.0%	0.787	26.8	97.7%	0.682

HT= Helical Tomotherapy, VMAT= Volumetric Arc Therapy, 3DCRT= 3 D Conformal Radiotherapy, Gy= Gray, CI= Conformity Index (CI=PIV/TV, where PIV= Prescribed Isodose Volume, TV= Target Volume), PTV= Planning Target Volume

After the completion of the systemic therapy, the patient was referred to radiotherapy for local adjuvant treatment. The planning CT was performed with the patient laying in a supine position, with his arms raised above his head, without using any immobilisation devices or respiratory motion management (therefore no ITV (Internal Target Volume) was contoured and Clinical Target Volume (CTV)-to-PTV margins were larger, in order to avoid geographical miss). He received a total dose of 25.5 Gy in 14 fractions on the tumour bed (CTV) plus a 1 cm margin, using a conformal helical intensity-modulated technique (Helical Tomotherapy).

Table 2. Dosimetric comparison for organs-at-risk

	HT		VMAT		3DCRT	
OAR	**Dmean (Gy)**	**Dmax (Gy)**	**Dmean (Gy)**	**Dmax (Gy)**	**Dmean (Gy)**	**Max (Gy)**
Spinal Cord	1.21	4.72	1.1	3.7	1.5	4.2
PRV_Spinal Cord	1.31	6.22	1.2	4.3	1.7	4.4
Heart	4.25	16.03	4.0	16.5	4.0	16.8
Lung_Left	10.59	28.43	9.9	26.9	12.8	26.5
Lung_Right	2.79	8.27	1.4	6.3	2.8	4.3
Lungs	6.21	28.43	5.12	26.89	7.15	26.55

Sternum	1.66	4.91	3.5	7.6	3.3	4.4
Scapula_Right	0.76	3.35	0.5	1.9	1.2	2.7
Scapula_Left	7.12	25.58	7.6	24.7	9.8	25.8
Nipple	0.27	0.4	2.1	2.3	1.4	2.5
Breast	3.86	6.46	9.4	15.2	14.7	20.2
Vertebrae	1.76	8.65	1.2	4.9	1.9	4.5

HT= Helical Tomotherapy, VMAT= Volumetric Arc Therapy, 3DCRT= 3 D Conformal Radiotherapy, Gy= Gray, PRV=planning risk volume, OAR= organ-at-risk

To ensure best target coverage, conformity, and homogeneity, as well as optimal healthy tissue sparing, two other comparative plans were calculated- one using VMAT (intensity-modulated/volumetric arc therapy) and another using a forward-planned, 3D conformal technique (**Figure 2**). Helical Tomotherapy showed better OAR sparing compared to 3DCRT and similar organ-at-risk dosimetry to VMAT, but better target dose homogeneity and conformity compared to both VMAT and 3DCRT. Overall, the helical tomotherapy plan proved to be of higher quality and thus was chosen for patient treatment. Table 1 shows a dosimetric comparison of the target and several organs-at-risk (Table 2) using the three different techniques. Radiotherapy was well tolerated, without acute toxicities. Following irradiation, the patient received a high-dose chemotherapy regimen and underwent autologous stem-cell transplantation. At his last follow-up visit (June 2022) the patient had a good overall status, with no signs of recurrence or severe adverse effects.

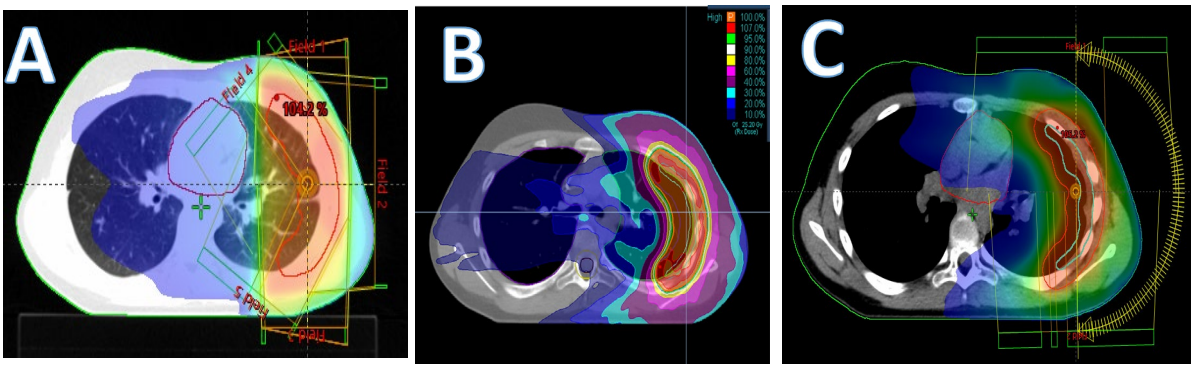

Figure 2. Dose distribution for the 3 comparative radiotherapy plans –
A. 3D Conformal Radiotherapy, B. Helical Tomotherapy, C. IMAT/VMAT/RapidArc

3. Discussions

The presented case is particular for several reasons. The patient was first treated in a county hospital and local radiotherapy was omitted at first diagnosis, despite the SIOP protocol's recommendation for flank irradiation in stage III intermediate-risk patients. The patient's subsequent disease presentation was not local but occurred as a pulmonary metastasis relatively early after completion of the initial treatment. Relapses usually occur within 2 years from diagnosis and are mainly solitary lung nodules. A distinct aspect of the first recurrence is the treatment, which was only systemic (chemotherapy), omitting local therapy such as surgery and/or radiotherapy which might also have been suitable treatment options at the time. The most peculiar feature of this case is the long 9-year disease-free period prior to the second relapse and the particular aspect of pleural involvement , with only a few similar cases reported in the literature (12–14). Thus, local control was good with no relapse in the flank, despite omitting local radiotherapy at first diagnosis. Being confronted with such a rare evolution of a nephroblastoma, the treatment was challenging, especially the local radiotherapy, with no guidelines for this particular clinical scenario. The dose

prescription was chosen taking into consideration both the whole lung irradiation doses that are usually delivered in metastatic Wilms disease, but also a boost dose to ensure local control. The systemic therapy was prescribed following several protocols, with different approaches (SIOP, COG, UKWR). Given the relatively good outcome of this patient, we can only assume that the tumour might have had some genetic/molecular favourable features. However, no molecular profile was performed for this patient, which, together with some gaps in the case documentation, we consider as limitations in this reporting. Future cases might benefit from genetic testing and molecular profiling, for a better risk stratification and personalized treatment. This case highlights the importance of multidisciplinary tumour board discussion of these patients, at presentation, which is an essential component of cancer management. Having all the stakeholders (pediatric surgeon, pediatric oncologist, radiation oncologist and others) discussing treatment strategy is known to increase treatment quality and improve outcome. Moreover, pediatric patients should be treated in specialized treatment centres, in a centralized manner, as recommended by several international bodies (15–17).

4. Conclusion

In conclusion, nephroblastoma (Wilms tumor) is a malignant tumor occurring in the kidney especially in pediatric patients. It requires a complex, multidisciplinary approach to ensure best treatment, with good outcomes and without excess toxicities. Several clinical prognostic factors influence outcome, together with the genetic landscape and treatment management. Relapse usually occurs early, mainly as pulmonary metastases, with late pleural metastasis being rare. Particular cases such as this one can present with late relapses, which raise several challenges regarding therapy, having no guidelines to cover such situations. For future cases, molecular testing could improve patient management and facilitate a personalized treatment, with possible better outcomes. Furthermore, multidisciplinary decision-making, and case centralization in specialized centres is essential in such peculiar cases.

Abbreviations:
AV – Actinomycin + Vincristine
COG – Children Oncology Group
CT – Computed Tomography
CTV – Clinical Target Volume
LOH – loss of heterozygosity
LOI – loss of imprinting
MRI – Magnetic Resonance Imaging
HT – Helical Tomotherapy
IMRT – Intensity-Modulated RadioTherapy
ITV – Internal Target Volume
PTV – Planning Target Volume
PRV – Planning Risk Volume
SIOP – International Society for Paediatric Oncology
UKWR – United Kingdom Wilms Relapse
VMAT – Volumetric Arc Therapy
WAGR – Wilms tumor, aniridia, genitourinary anomalies, and intellectual disability (mental retardation)
WT – Wilms Tumour

Statements:
Authors' contributions:
AT – conceptualization, data collection, manuscript writing
CD, GV, CG, CB– manuscript revision, part of the patient treatment management team

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Approach to Treatment for Breast Cancer Metastasis To the Orbit: A Case Report

Adrian-Marian Radu[1], Ana Băncilă[2]

[1] *Radiotherapy Department, „Prof. Dr. Alexandru Trestioreanu" Oncology Institute, Bucharest, Romania*
[2] *Radiotherapy Department, Neolife Clinic, Bucharest, Romania*

Corresponding author: Adrian-Marian Radu; **e-mail**: adrianradu1995@yahoo.com

Abstract

Breast cancer is the most common cancer worldwide and, despite its well-known ability to spread to multiple anatomic sites, orbital metastases are considered an exceptional event.

We present the case of a 53-year-old woman who was diagnosed with luminal B cT4cN1M1 breast cancer with lung metastases (M1PUL) and bone metastases (M1OSS) and was treated with palliative chemotherapy, zoledronic acid, and hormonotherapy with no significant benefit (progressive disease).

Two years after the diagnosis, the patient complained of right eye proptosis, local pain and decrease in visual acuity. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a soft tissue mass in the right orbit, extending along the right optic nerve, but not invading it. A multidisciplinary team determined that the best next therapeutic step is orbital palliative radiotherapy. Stereotactic body radiation therapy (SBRT) was used because of the location of the metastasis and the high risk of vision loss. Proptosis and local pain were resolved two months after palliative SBRT and an imaging partial response was obtained.

Keywords: *breast cancer, orbital metastasis, radiotherapy, SBRT*

Case Reports

1. Introduction

Intraorbital metastases are rare, representing 1-13% of the orbital tumors (1,2). Breast cancer is the main primary tumor that metastasizes intraorbitally. In 12 to 31% of the affected patients, intraorbital metastasis was the initial clinical presentation (3,4). An analysis of the histopathologic characteristics of the intraorbital metastasis reported a higher incidence of the luminal subtype of ductal carcinoma, probably explained by the high number of estrogen receptors of the periorbital soft tissues (5). An increased propensity was observed for the lobular type, as compared with the invasive ductal carcinomas (6).

Radiotherapy is the established palliative treatment for orbital metastases, with modern techniques such as SBRT, allowing for the administration of maximal doses of targeted radiation while avoiding the organs at risks and thus, minimizing potential serious adverse events (cataract, radiation retinopathy, neuritis) (7).

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2. Case report

2.1. History

A 53 year old patient, without significant personal or family medical history, presented to the emergency department in September 2020 with an ulcerated mass at the junction between the superior inner and outer quadrants of the right breast, associated with hard and freely mobile axillary lymphadenopathy on the soft tissue planes. The mammography described a 77/57 mm spiculated, polilobated nodule with associated micro-calcifications, infiltrating the skin and pectoral fascia. In the axilla multiple lymph nodes with a maximum size of 10/16 mm were observed. The ultrasound-guided biopsy of the breast mass and right axillary adenopathy confirmed the diagnosis of invasive moderately differentiated G2 ductal carcinoma, luminal B subtype, with lymph node metastases. The native and contrast-enhanced cerebral and thoracic-abdominal-pelvic (TAP) CT showed multiple lung nodules suggestive of secondary dissemination, osteolytic lesions in the left coccyx and the thoracic-lumbar vertebrae, which were confirmed by scintigraphy as metastatic disease. The patient was staged as stage IV, cT4cN1M1 (M1OSS, M1PUL) and started on hormone therapy (Letrozole), targeted therapy with cyclin-dependent kinase (CDK) 4/CDK6 inhibitors (Palbociclib) and osteoclasts inhibitors (Zoledronic acid). In January 2022, the follow-up CT scan showed peritoneal nodules and the treatment was changed to Ribociclib and Fulvestrant.

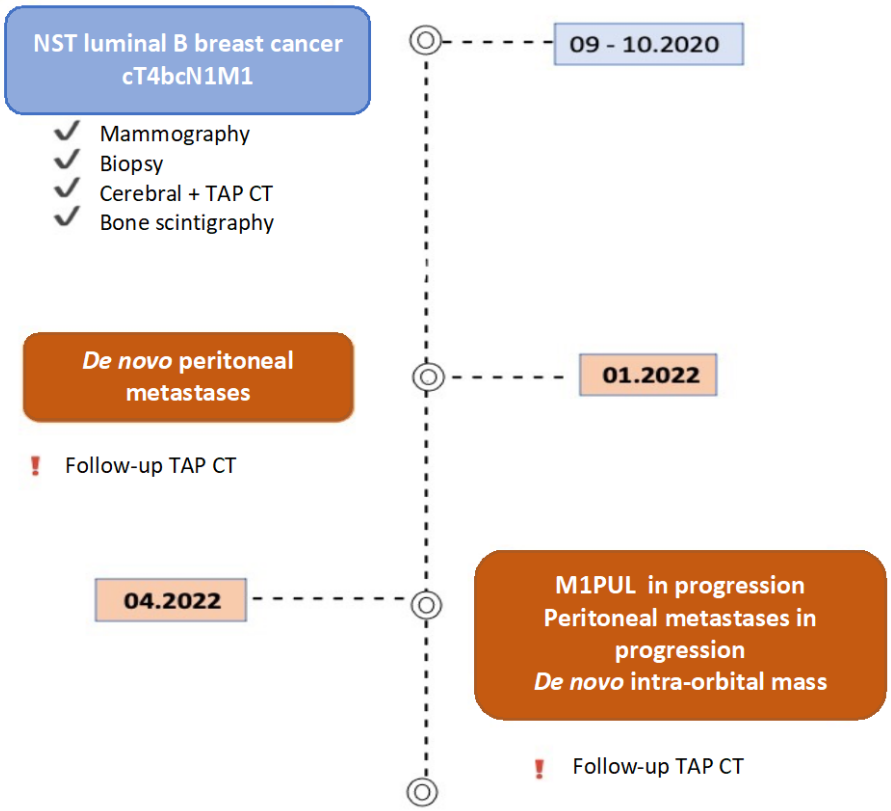


Figure 1. Patient's history

In April 2022 the patient presented with mild exoftalmia, ocular pain and impaired visual acuity in the right eye. The CT scan showed a de novo mass involving the right orbit, and a contrast-enhanced MRI scan was performed. It described a 15/15 mm intra-orbital lesion in contact with the right optic nerve and the right inferior rectus muscle, probably invading the latter. The lesion had malignant characteristics, such as inhomogeneous contrast enhancement (Fig. 4A). The treatment regimen was changed to weekly Paclitaxel and Fulvestrant, which remains the patient's current treatment.

2.2. Treatment approach

Palliative stereotactic radiation was chosen for its ability to achieve a quick response to treatment, as well as due to the location of the target volume. Slices of 1.25 mm thickness were acquired using a CT simulation in the supine position with a thermoplastic mask as a contention device and the images were combined with those from the prior cerebral MRI. The planning target volume (PTV) was created by using the gross-tumor-volume (GTV) as the target volume and adding a 1 mm safety margin. Intensity-Modulated-Radiation-Therapy (IMRT) was delivered using a True-Beam-Agility multileaf collimator (MLC). The prescribed dose was 18 Gy in 3 daily fractions, calculated at 80% isodose on the PTV. Image-guided radiotherapy (IGRT) using daily cone-beam CT (CBCT) increased the reproducibility and accuracy of the administration. Five arches treatment planning allowed the dose reduction to the organs at risk, especially for the right optic nerve, situated in the proximity of the target volume. Dose constraints for all the organs at risk (optic nerves, optic chiasm, lens, ocular globes and brain) were respected, including for the right optic nerve (15.2 Gy in 0.2 cm^3) (8).

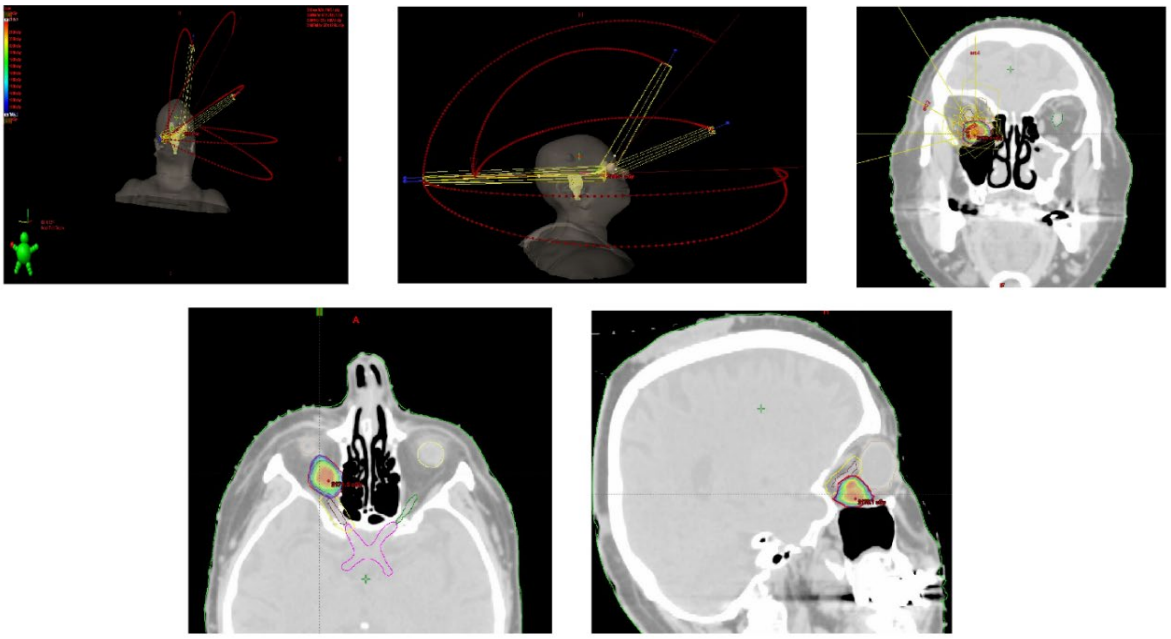
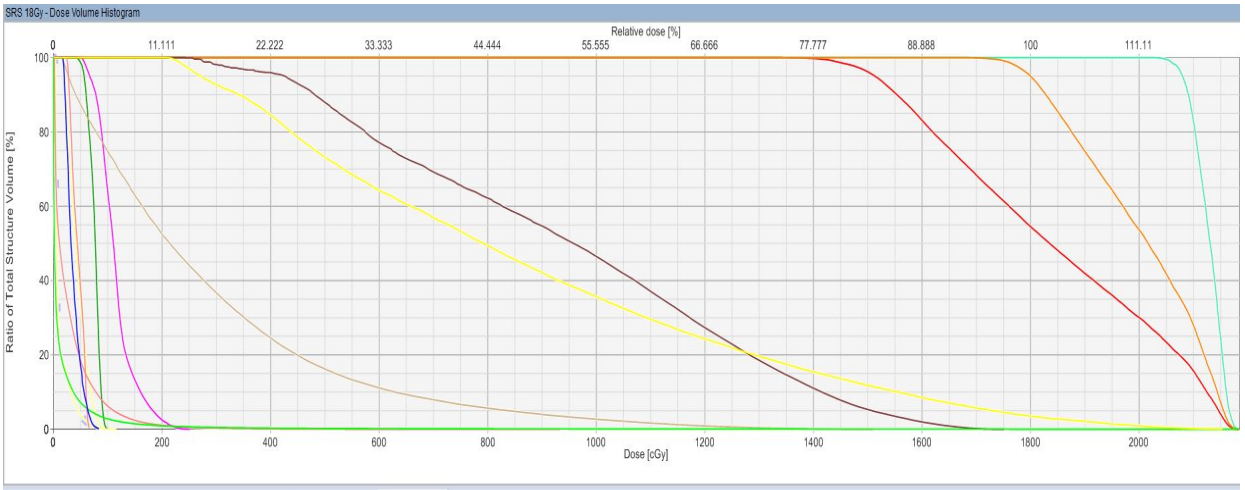


Figure 2: The spatial distribution of the five dose administration arches. A hot spot of 21,7 Gy within the irradiation volume.

2.3. Follow-up

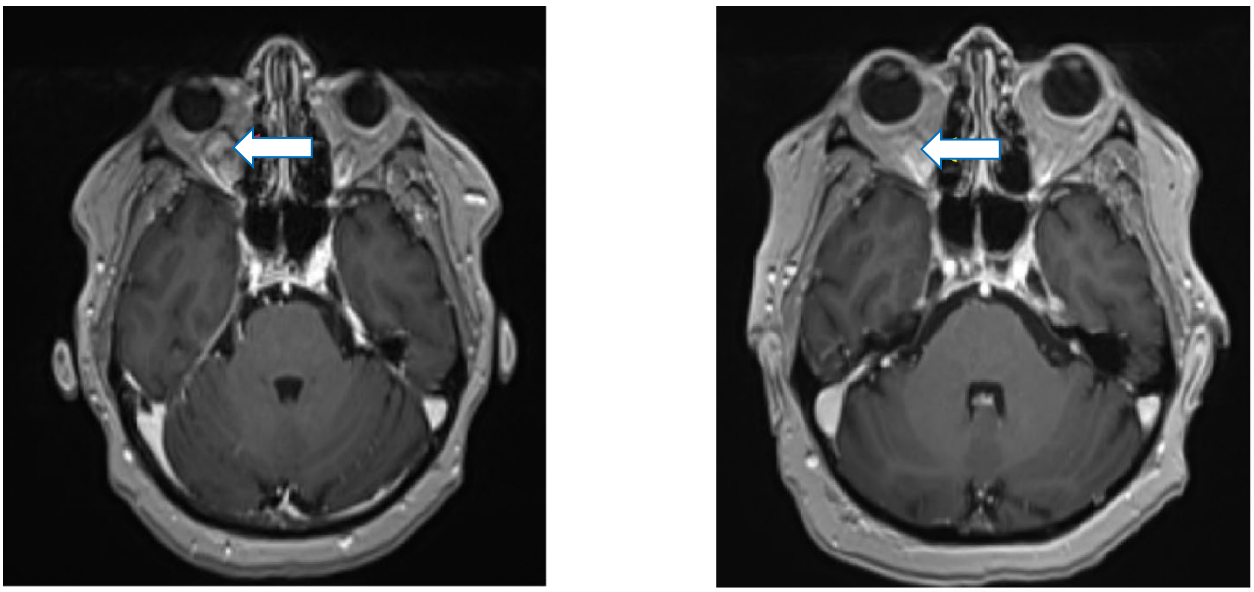
No adverse events were reported during the stereotactic body radiation therapy (G0 according to CTCAE 5.0-Common Terminology Criteria for Adverse Events). Contrast-enhanced cerebral MRI was performed 2 months after last SBRT, and showed regression of the right intraorbital nodule as compared to the pre-stereotactic MRI exam (12/7 mm vs. 15/15 mm, partial response, according to RECIST 1.1 criteria) (Fig. 4B). The ocular pain and exophthalmia also improved. Follow-up MRI is now scheduled every 3 months in the first year, every 6 months in the next 2 years and annually in the following 3 years. An annual ophthalmological examination to assess visual acuity was also recommended as part of the short and long-term follow-up.



Dose Prescription | Field Alignments | Plan Objectives | Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum

DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
	BODY	Approved	SRS 18Gy	C1	8446.7	100.0	100.0	0.0	2185.1	15.2
	Brain	Approved	SRS 18Gy	C1	1371.5	100.0	100.0	1.2	934.1	29.3
	Brain Stem	Approved	SRS 18Gy	C1	30.7	100.0	100.0	2.8	116.1	12.0
	Dose 119[%]	Approved	SRS 18Gy	C1						
	Eye L	Approved	SRS 18Gy	C1	8.6	100.0	100.0	11.5	97.4	43.6
	Eye R	Approved	SRS 18Gy	C1	8.9	100.0	99.9	12.7	1509.6	288.2
	GTV	Approved	SRS 18Gy	C1	1.7	100.0	99.7	1667.5	2185.1	1999.3
	GTV_CORE	Approved	SRS 18Gy	C1	0.5	100.0	99.9	2025.5	2185.1	2127.6
	GTV_RING	Approved	SRS 18Gy	C1	1.2	100.0	100.4	1681.5	2171.5	1956.3
	LENS	Approved	SRS 18Gy	C1	0.3	100.0	100.8	17.3	85.7	40.7
	Lens L	Approved	SRS 18Gy	C1	0.2	100.0	100.5	23.7	66.0	44.6
	Lens R	Approved	SRS 18Gy	C1	0.2	100.0	101.3	16.9	85.5	36.2
	OPT_R+2MM	Approved	SRS 18Gy	C1	2.7	100.0	99.9	207.2	2155.0	871.0
	Optic Chiasm	Approved	SRS 18Gy	C1	0.7	100.0	99.9	49.5	251.0	114.2
	Optical Nerve L	Approved	SRS 18Gy	C1	0.6	100.0	99.4	42.5	102.2	75.5
	Optical Nerve R	Approved	SRS 18Gy	C1	0.6	100.0	100.0	242.6	1752.4	943.7
	PTV	Approved	SRS 18Gy	C1						
	PTV_HR	Approved	SRS 18Gy	C1	3.0	100.0	100.0	1312.6	2185.1	1838.6

Figure 3. Treatment Dose-Volume Histogram (DVH).



A. **B.**

Figure 4. Contrast-enhanced MRI (T1, Axial Section): intra-orbital, extra-cone mass in the right orbit before SBRT (A) and after SBRT (B).

3. Discussion

The particularity of this case resides in the intraorbital localization of the metastasis, rapid need for management and lack of any other palliative treatment that would allow preservation of vision. This patient was not a surgical

candidate due to the tumor's direct contact with the right optic nerve and the lack of a separation plan from the right inferior rectus muscle by imaging. Thus, the stereotactic radiotherapy was considered appropriate as a palliation treatment.

Because the orbit is an unusual metastatic site, the number of studies on stereotactic irradiation of orbital metastases is relatively low, with a reduced number of patients included in each study. In a retrospective study conducted by Klingenstein A *et al*. on 14 patients treated with a radio-stereotactic method similar to the SBRT, CyberKnife, the irradiated tumor volume ranged from 0.2 to 35 cm^3, with dosages of 16.5-21 Gy (median of 18 Gy, average of 18.2 Gy) and the stabilization or regression of orbital metastasis was obtained in 87% of cases (9).

In a retrospective study conducted between 2012-2016 by Riva G *et al.,* 21 patients with 24 intra-orbital metastases treated with SBRT were included. The median dose was 18 Gy (15-24 Gy), administered in 2-3 fractions with a median dose/fraction of 6 Gy. The average follow-up was 6.2 months (1.1-30 months) and 16 out of 24 orbital lesions had no local recurrence. Post-treatment symptoms were improved in all patients. Grade 1 acute toxicities were reported in 33% cases of irradiated tumors, and the most frequently reported ones include: conjunctival erythema (75%), epiphora (37%), and superior palpebral oedema (25%). No grade 2 toxicities were reported and only 1 patient developed a long-term adverse event, ipsilateral cataract (10).

In 2008, Hirschbein *et al.* performed a retrospective analysis of CyberKnife-SRT (stereotactic radiotherapy) in 16 intraorbital lesions (9 of which were malignant). SRT was delivered in 2-5 fractions up to a mean dose of 20 Gy. A decrease or stabilization in the lesion's size was registered in all patients who underwent radiological post-SRT evaluation after a mean follow-up of 7 months (11). In another retrospective report published by Mehta *et al*., 13 lesions near the anterior visual pathways were treated with CyberKnife-SRT in 2-5 fractions with a total mean dose of 21.7 Gy; all patients had post-SRT local control without deterioration of the visual pathway (12).

In a retrospective clinical evaluation conducted by Desheng Xu at al. on 202 patients treated with GammaKnife-SRT with dosages of 10 to 40 Gy (202 lesions, 82 of which malignant) the tumor volume irradiated ranged from 0.04 to 35 cm^3. The follow-up ranged from 12 to 114 months and the local control was obtained in 93.6% of patients.

Post-treatment symptoms were improved in all patients. Grade 1 acute toxicities were reported in 9.4% cases (mostly transient conjunctival edema) (13).

Table 1. Stereotactic Radiotherapy for the treatment of orbital lesions (orbital metastases included); LC= local control, R- retrospective, pts= patients.

Study	Patients (no. of lesions)	Follow-up (months)	Treatment	Total Dose (range)	Outcome	Toxicity
Klingenstein A. et al. (2012,R)	14 (16, all metastases)	6 (mean)	CyberKnife	16.5-21 Gy in 1 fx	LC 87%	No adverse effects during follow-up.
Hirschbein M.J. et al. (2008,R)	16 (16, 9 malignant)	7 (mean)	CyberKnife	10-25 Gy in 2-5 fx	LC 100%	1 pt G1 (nausea)
Mehta V.K. et al. (2002,R)	13 (13, 3 malignant)	18 (median)	CyberKnife	17.8-25 Gy in 3-5 fx	LC 100%	N/A
Riva G. et al. (2018,R)	21 (24, all metastases)	6.2 (median)	CyberKnife	15-24 Gy in 2-3 fx	LC 100%	8 pts G1 (75% conjunctival erythema 37 % increased tearing 25% upper eyelid edema) No ≥ G2
Xu D. et al. (2010,R)	202 (202, 82 malignant)	34.5±14.7 (median)	GammaKnife	10-40 Gy in 1-2 fx	LC 93.6%	19 pts G1 (transient conjunctival edema)

In the case of stereotactic radiation treatment of orbital lesions, the main concern remains radiation induced optical pathway neuropathy. In a retrospective study conducted by Stafford *et al*. which included 215 patients treated with single stereotactic radiotherapy for benign tumors of the sellar or parasellar regions, the rates of optic nerve neuropathy were 1,7% when the dose was less than 8 Gy, 1,7% when it was between 8 and 10 Gy, and 6,9% when the dose was in excess of 12 Gy (14). For the current case, the mandatory optic pathway constraints for SBRT in 3 fractions established by the latest trials and studies were applied: D_{Max} (0,1cm^3)<15Gy and D(0,2cm^3)< 15.3Gy (8,16-20).

SBRT gradually improves its status of optimal palliative treatment for orbital metastases, implying less risks as compared to surgery (15). In addition, the shorter period of treatment as opposed to conventional radiation therapy may be crucial in saving the vision of a stage IV oncological patient.

4. Conclusion

The orbital metastases continue to be a challenge for the short-term management of the oncologic patient due to their close anatomic relationship with radio-sensitive organs, requiring rapidly implemented treatment, without which imminent vision loss is likely to occur. The scientific and technological advances in radiotherapy allowed for the rapid and optimal approach of these metastases and SBRT represents a quick, safe and efficient method for the management of the orbital metastases.

Abbreviations:
CT – computed tomography
MRI – magnetic resonance imaging
SBRT – Stereotactic Body Radiation Therapy
GTV – gross tumor volume
LC – local control
PTV – planning tumor volume
IMRT – intensity-modulated radiation therapy
M1OSS – bone metastases
M1PUL – lung metastases
MLC – multileaf collimator
IGRT – image-guided radiation therapy
CTCAE – Common Terminology Criteria for Adverse Events
OS – overall survival
RECIST – Response Evaluation Criteria in Solid Tumor

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Informed Consent: The informed consent was obtained from the patient for publication and any accompanying images.
Ethical Approval: The treatment strategy was approved by Neolife Clinic's tumor board and ethics committee.

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Acute Tuberculosis Infection Concomitant with Nivolumab Treatment in a Patient with Non-small Cell Lung Cancer: A Case Report and Review of the Literature

Edvina E. Pîrvu[1], Cristina E. Cocioabă[1]

[1] *Medical Oncology Department, Colțea Clinical Hospital, Bucharest, Romania*

Corresponding author: Edvina E. Pîrvu; **e-mail**: edvinapirvu@gmail.com

Abstract

Nivolumab, a fully human immunoglobulin G4 (IgG4) monoclonal antibody PD-1 immune checkpoint inhibitor and other immune checkpoint inhibitors are used to promote activation of anti-tumor immuno response in the fight against cancer. Recently published case reports raised awareness on a particular adverse effect of immunotherapy: reactivation of latent Mycobacterium tuberculosis infection. This case report describes a 67-year old Caucasian male who presented with concomitant tuberculosis infection of the pleura and pericardium with nivolumab therapy for non-small cell lung cancer. He received antituberculous treatment, with favorable evolution. With no available guidelines for the management of tuberculosis during PD-1/PD-L1 blockade, a high index of suspicion should exist when the evolution of the patient takes an unexpected turn. This approach should be applied especially in countries with a high incidence of tuberculosis.

Keywords: *checkpoint inhibitors, non-small cell lung cancer, tuberculosis, case report*

Case Reports

1. Introduction

Immune checkpoint inhibitors are transforming lung cancer treatment, providing long-lasting responses and improved survival, but with a new spectrum of toxicities. The modulation of the immune response due to immune checkpoint inhibitors and the immune depression induced by cancer can reactivate latent tuberculosis (TB) via excessive tumor necrosis factor-α (TNF-α) secretion (1,2). The diagnosis of tuberculosis could be challenging, with many non-specific symptoms such as weight loss, anorexia, cachexia, new interstitial infiltrates possibly owing to both cancer progression and infection. Case reports of tuberculosis reactivation under immunotherapy are increasing in the medical literature with two theoretical hypotheses that could explain this phenomenon: a hypersensitive response similar to immune reconstitution inflammatory syndrome or immune checkpoint–related lymphopenia (3).

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2. Case presentation

We present the case of a Caucasian male undegoing trearment for advanced-stage lung cancer, and who, following three months of nivolumab treatment developed tuberculous pericarditis and pleurisy. Romania is a country with a particularly high prevalence of tuberculosis. Thus, this case adds to the current medical literature on the association of nivolumab therapy for advanced cancer with the concomitant development of acute tuberculosis.

Main characteristics & concerns: A 67-year-old former smoker male presented in July 2016 with weight loss (5 kilograms in 2 months), coughing and progressive dyspnea. The symptoms developed insidiously in the last 8 weeks.

Comorbidities & interventions: The patient had moderate obstructive airway disease as a result of a 35-pack-year history and a history of duodenal ulcer, no personal familial history of cancer and no exposure to occupational carcinogens. He was an occasional drinker. He had no known drug allergies and was on home medication with pantoprazole 40 mg/day.

Examination & investigations: At presentation, the patient was evaluated using the Eastern Cooperative Oncology Group (ECOG) scale and had a performance status (PS) of 1. Clinical examination revealed reduced air entry and dullness to percussion in the right upper lung. He was afebrile, with a good nutritional status. The chest radiography showed a 3 centimeters spiculated mass in the apex of the right lung. Haemato-biochemistry screening was within normal range. Due to the high suspicion of cancer, a diagnostic mediastinoscopy with biopsy of the nodal station 4 R was performed. Computed tomography (CT) scans of the head, thorax and abdomen performed for staging established the stage as T2N3M0 (Figure.1).

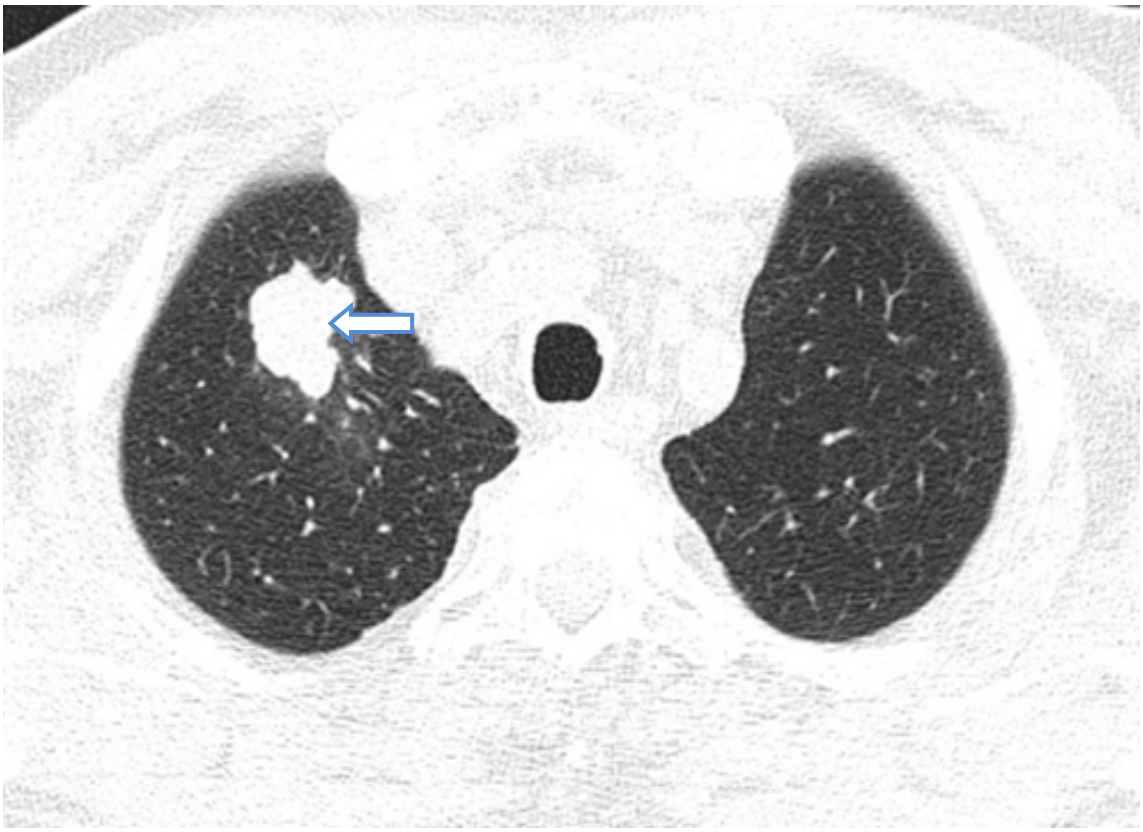

Figure 1. CT Exam at Diagnosis Showing a Mass in the Apex of the Right Lung.

Diagnosis: The histology showed a moderately differentiated adenocarcinoma with an immunohistochemical profile, which was consistent with lung cancer (CK7-positive, CK20-negative, and TTF1-positive).

Treatment and Outcomes: The case was discussed with the multidisciplinary cancer care team and according to the standard of care at the time, the patient received definitive chemoradiation with a regimen consisting of taxane and platinum salt, that it is known from previous studies to provide a better survival compared with sequential chemoradiation (4).

From October 2016 he started chemotherapy with paclitaxel 175 mg/m2 and cisplatin 75 mg/m2 in day 1, every 3 weeks, for 4 cycles, concurrent with radiotherapy to a total dose of 66 Gray in 33 fractions (Figure 2). Towards the end of the treatment, the patient presented severe hematologic toxicities (grade III anemia, grade III thrombocytopenia, grade II neutropenia), which required admission to the hospital and blood transfusion, with full recovery.

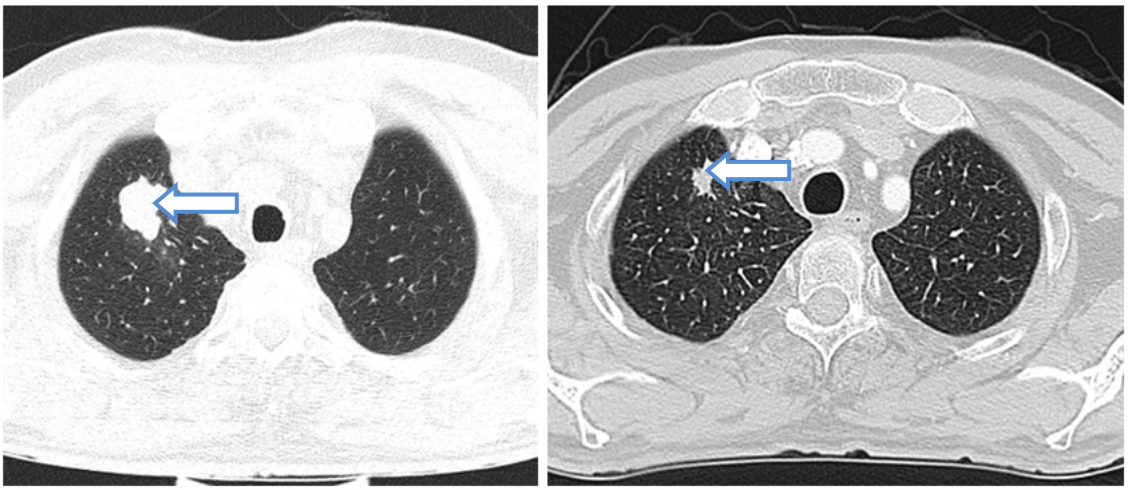

Figure 2. CT Exams Comparing the Pulmonary Mass at Diagnosis (right) and the Pulmonary Mass after Chemoradiation (left).

In February 2017, a follow-up CT of the thorax described new pseudo-nodular lesions in the lower lobes. The patient was asymptomatic. He was referred to pulmonology to exclude an infection. Cultures were negative for Gram-positive and Gram-negative bacterium and Koch's bacillus. At the time of progression to metastatic disease, the tumor was tested and was negative for ALK fusions and EGFR mutations. No PDL-1 testing was available in Romania at that time and immunotherapy was not approved in the first line metastatic setting. Due to previous toxicities, pemetrexed monotherapy 500 mg/m2 every 3 weeks was started in April 2017, with clinical benefits (no dyspnea and 3 kilograms weight gain). The sequential CT scans indicated stable disease, and the patient had a good tolerance to this treatment for 18 months, when the primary tumor and mediastinal lymph nodes showed progression on imaging.

In November 2018 nivolumab monotherapy 240 mg every 2 weeks flat dose was initiated. After three months, a CT scan was performed to evaluate the response to treatment. It described regression of the primary tumor, mediastinal nodes and pulmonary metastasis, with bilateral pleurisy and pericardial effusion (Figure 3). Diagnostic and therapeutic pericardiocentesis and thoracentesis were performed, and the fluids were diagnosed as exudates, with frequent lymphocytes, frequent reactive mesothelial cells and rare erythrocytes. Because both pericardial and pleural fluid collections were rapidly growing, with persistent dyspnea, the patient was referred to thoracic surgery. In May 2019 the patient underwent left thoracoscopy, with pericardial window and pleural biopsy. The pathology report from the pericardium and pleura described fibro-adipose tissue with epithelioid granulomas and chronic inflammatory infiltrate. Subsequently, a quantiFERON TB test was performed, which detected the presence of Mycobacterium tuberculosis.

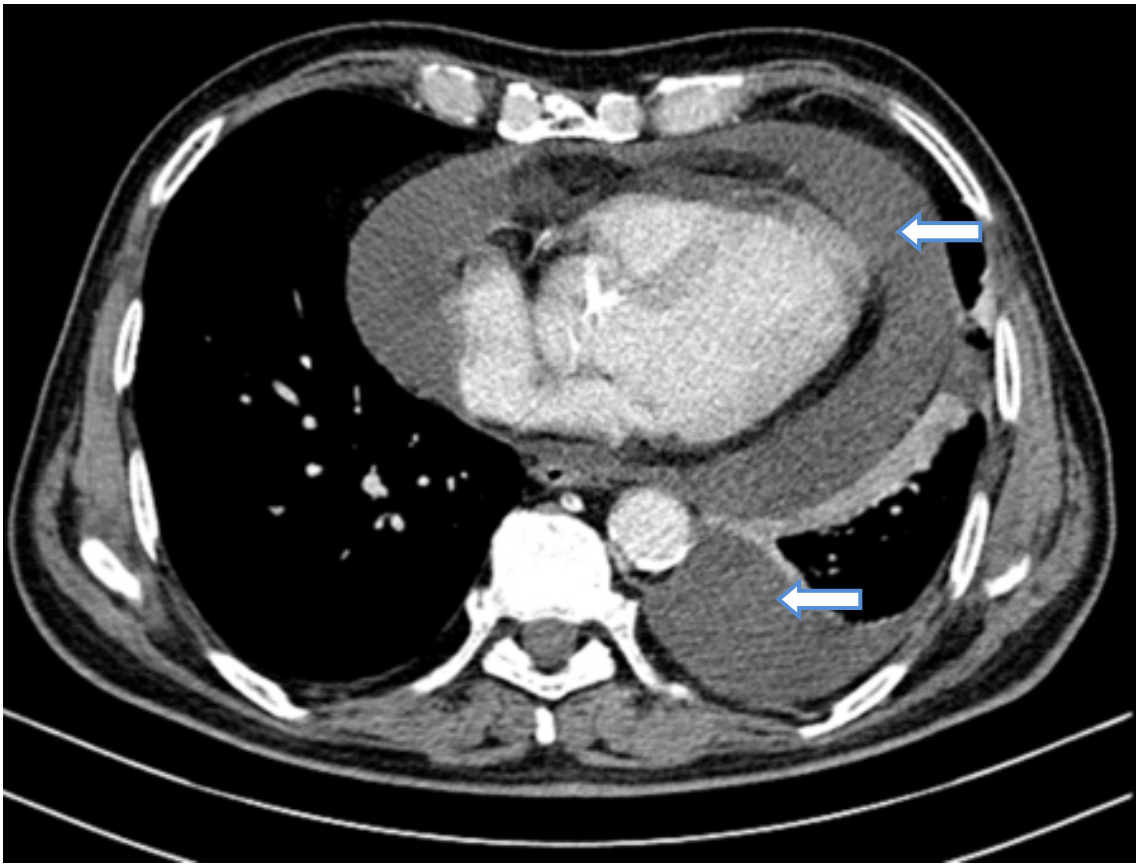

Figure 3. CT exam Showing Pleurisy and Pericardial Effusion After the Initiation of Treatment with Nivolumab.

Based on the positive result and knowing that the most common cause of granulomatous inflammation worldwide is tuberculosis (5), with Romania being highly endemic, the pulmonologist started the patient on antituberculous treatment. The treatment was initiated in June 2019 and consisted of rifampin 600 mg/day, isoniazid 300 mg/day, ethambutol 1200 mg/day and pyrazinamide 1500 mg/day for 6 months concomitant with prednisolone 32 mg/day for the first 30 days. Nivolumab was stopped during the first month of antituberculous treatment and reinitiated in July 2019 at the same dose, with complete resolution of the pleural and pericardial effusions on serial CT scans and echocardiograms and with significant clinical benefit; the patient was asymptomatic.

Follow-up: The patient sustained partial radiological response on the primary tumor, mediastinal nodes and pulmonary metastasis, with no evidence of progression, and with excellent treatment tolerance until January 2021, when he progressed on the primary tumor and pulmonary metastasis after 26 months of stable disease on nivolumab. Docetaxel 75 mg/m2 monotherapy was started for a total of 4 cycles. Unfortunately, the patient progressed soon after the treatment ended, with severe deterioration of the performance status and succumbed to his death in July 2021.

3. Discussion

Strengths & limitations: The current case report, is the first one in Romania which to our knowledge describes reactivation of tuberculosis during nivolumab therapy for non-small cell lung cancer. However, a diagnosis bias for TB may be raised by the lack of a positive TB culture from the patient's pleral and pericardial fluids. On the other hand, the association between biopsy proved granulomatous inflammation involving mediastinal lymph nodes and a positive quantiFERON TB test combined with a favorable response to anti TB therapy provides important arguments in favor of an ongoing TB infection. In this patient, interpreting the pleural

and pericardial fluid collections as progressive disease would have been an error with potential fatal consequences. In countries with limited resources, where the possibilities to rebiopsy in the metastatic setting are scarce, a paradoxical response should always be interpreted with caution and, if possible, a new biopsy should be performed. Discussing the case in the multidisciplinary team allowed for a correct diagnosis and prompted timely initiation of antituberculous treatment, with favorable outcomes.

Medical Literature: The rate of tuberculosis among cancer patients receiving anti-PD1/PD-L1 agents was estimated to 1 in 1000 patients according to the French prospective registry managed at the Gustave Roussy Cancer Center (6). Giving the significantly higher incidence of tuberculosis in Romania (74/100 000 in 2016) (7), a higher rate of tuberculosis among patients treated with immunotherapy is expected. Unfortunately, in Romania currently there is no functional cancer registry; hence no data on the rate of tuberculosis among cancer patients receiving immunotherapy is available. Additionally, there are no regional guidelines to address this challenging association.

According to 2018 World Health Organization (WHO) guidelines (8), cancer patients are not included in the screening of latent tuberculosis due to the lack of evidence. However, increasing evidence suggests a significantly high correlation between the PD-1/PD-L1 blockade therapy in cancer patients and the incidence of active TB. (9,10,11). A recent systematic review showed that the TB rate in patients receiving PD-1/PD-L1 blockade therapies was 2,000 cases per 100,000, a rate that was 35 times higher than in the general population. Moreover, the mortality rate of the infected patients was considerably higher than currently expected (in the 18 patients for whom the clinical outcome was recorded, 77.8% were cured or achieved remission, and 22.2% died of TB).

Overall, the systematic review suggests that the administration of PD-1/PD-L1 blockade therapies to patients interfered with the immunologic control of latent TB infections, that led to increased activity of tuberculosis bacilli and active TB disease (12). The mechanism behind this association remains elusive. In the majority of exposed individuals, a stable relationship forms between host immune cells and Mycobacterium Tuberculosis (MTB) preventing disease progression. However, an emerging concept is that an excessive immune response to MTB may be equally harmful. Hence the anti PD-1/PD-L1 therapy may contribute to TB reactivation. For instance, a recent study revealed that hypoxia within TB lesions led to the up-regulated expression of PD-1/PD-L1 axis proteins. Meanwhile, results of another study focusing on PD-1/PD-L1 blockade immunotherapy indicated that inhibition of this pathway could stimulate multiple types of immune cells within granulomas (i.e. T cells, macrophages, dendritic cells), thereby resulting in granuloma collapse and excessive immunopathology. These results are consistent with the results of studies of MTB-infected patients and of human 3D cell culture-based TB models that suggest that PD-1 inhibition accelerates MTB growth via excessive TNF-α secretion. Taken together, these results highlight the important role of PD-1 in fine-tuning the balance between pro- and anti-inflammatory responses against tubercle bacilli to avoid tissue damage (2,13). Intra-granulomatous hypoxia has been described as a possible intimate correlative factor. PD-1 and its ligand PD-L1 are expressed in human granulomas suggesting a regulatory role at the site of disease (14), TB granulomas are hypoxic and PDL1 is up-regulated by hypoxia further suggesting a mechanistic link between hypoxia and the PD-1/PD-L1 axis within TB lesions (15)(16). Preclinical data showed that hypoxia increases the expression of PD-1 and its ligands, and that PD-1 inhibition increases MTB growth (2). TNF- α seems primarily responsible for this effect whereas TNF- α neutralization reverses the anti-PD-1 induced phenotype (17). Taken together all this new incoming information may sustain the recommendation for routine monitoring of latent TB in patients receiving ICIs-based immunotherapies (12).

Generally, in the case of active tuberculosis, immunotherapy is interrupted for a limited period of time, as well as any further immunosuppression while the anti-tuberculosis treatment is promptly started. Since there is no guideline, the exact moment of (re)starting the

PD-1/PD-L1 inhibitors after the adequate anti-TB treatment is not known; nevertheless, the literature suggests resuming or initiating immunotherapy 2–4 weeks after anti-tuberculosis treatment. Additionally, the hepatic toxicity of antituberculostatic drugs should be considered and monitored carefully (18).

4. Conclusions

To the best of our knowledge, this is the first case report in Romania of an acute TB infection during immunotherapy in a patient with lung cancer. The anti-TB specific treatment was effective and allowed for the continuation of nivolumab with a good and durable clinical response. Emerging data confirm that tuberculosis reactivation can occur during immunotherapy and it must be actively monitored allowing for a timely diagnosis and initiation of specific treatment, particularly in countries with a high TB incidence. Involvement of the multidisciplinary team early in the course of the disease is essential for the correct diagnosis and management of such cases.

Abbreviations:
ALK – anaplastic lymphoma kinase
CK 7 – cytokeratin 7
CK 20 – cytokeratin 20
CT – computed tomography
ECOG – eastern cooperative oncology group
EGFR – epidermal growth factor receptor
ICIs – immune checkpoint inhibitors
MTB – mycobacterium tuberculosis
PD-1 – programmed cell death protein 1
PD-L1 – programmed death ligand 1
TB – tuberculosis
TNF- α – tumor necrosis factor alfa
TTF1 – thyroid transcription factor 1
WHO – world health organization

Statements:
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Ethical Approval: The treatment strategy was approved by the institutional/local tumor board (name).

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High Tech – High Touch – the Two Sides of Radiation Oncology

Monica-Emilia Chirilă[1], Alessio Giuseppe Morganti[2,3]

1 Mvision AI, Helsinki, Finland

2 Radiation Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, 40138 Bologna, Italy.

3 Radiation Oncology, Department of Experimental, Diagnostic and Specialty Medicine, Alma Mater Studiorum University of Bologna, 40138 Bologna, Italy.

Interview

Professor Alessio Giuseppe Morganti teaches at the University "Alma Mater Studiorum" from Bologna . He is an expert in radiotherapy of prostate cancer and gastrointestinal malignancies (rectal, pancreatic and biliary tract cancers), and in palliative care. He was the principal investigator in more than 50 clinical studies and published more than 400 papers in Scopus- indexed journals.

He kindly agreed to share his view about current aspects of Radiation Oncology.

MC: Professor Morganti, what is your opinion on the technological advancement in radiotherapy?

AGM: We have good news, indeed, most of them due to the technological advances, which allow us to use a higher dose to treat the tumor while keeping the risk of treatment-related toxicity at the same level. there are several examples of this (1).

However, sometimes I think our enthusiasm for new technologies and tools – artificial intelligence – radiomics - is exaggerated. I was asked once which the best technology in Radiotherapy is. So, I showed a picture of a Cobalt machine, used by a colleague from an African country. He also uses a classical simulator, based on fluoroscopy. This African colleague told me that it happens many times that a urologist calls him at the end of the working day for a prostate cancer patient who has a painful bony metastasis that needs palliative Radiotherapy. So, he frequently arrives home 20 minutes late because of this emergency that he has to solve. Twenty minutes - which includes seeing the patient, simulation, planning and treatment delivery. In my environment, I am absolutely unable to treat a patient in such a short time, having to proceed with all the phases from which we are now unable to ignore (CT-simulation, contouring, treatment planning, image-guidance, and so on). Therefore, I should conclude that, at least in that setting, 2D radiotherapy is the most practical and efficient way to quickly treat a symptomatic patient. I see in my

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daily practice my younger colleagues doing a carefully planned VMAT for a similar case. Do we really need to do that? Are we using our resources wisely? Do we always need the latest technology? I believe that many times we buy machines from which we use only half of their technical possibilities, and some other times we use a newer technology even if it would not be really necessary.

MC: Since you mentioned the benefits of implementing new technologies, do you see any possible disadvantages?

AGM: One of the disadvantages of focusing on technology is to lose sight of the clinical part. For example, clinical research on pancreatic cancer is mainly focus on any – even very small -benefits in terms of survival, but with a low interest about the benefit in terms of quality of life. Sometimes what we offer are a few more weeks in which the patients are highly symptomatic and have a poor quality of life. When assessed in a study, the quality of life is mentioned only as something of secondary importance, and I believe we should take this aspect into account in research and also in clinical practice. A recently published paper reported on the quality of pain management in radiotherapy departments by analyzing the analgesic prescriptions and concluded that almost half of the cancer patients had suboptimal pain management (2).

MC: What could be the cause of this situation?

AGM: I would say there is a lack of training and education on pain management. I saw in my daily practice that my residents should improve their knowledge in this field. To compensate for that, I tried to invite specialists to give lectures on this topic, to improve juniors' skills in symptoms and particularly pain management. But sometimes, the specialists have the tendency to get into details on the pathophysiological aspects of pain, and the simple practical message that the trainees need might be partially lost.

MC: Could it be also because of some patients hesitate to use opioids? We sometimes see the fear of tolerance or addiction and the fact that they perceive it as a sign of terminal disease, and this thought can be disturbing, and as a result, rejected.

AGM: Indeed, we see this situation in our clinical practice, but these misconceptions can be overcome by talking to patients and providing information and support. One recent study proved this concept by showing that pain control was significantly better in patients who, in addition to the pharmacologic (and radiotherapy treatment) had also a discussion with a nurse, regarding the causes of the pain and the way they can manage it (3).

MC: This example of the positive impact of the discussion with the patient makes me think of the importance of psychologists in oncological care.

AGM: The psychologist's work is important, without a doubt, but also in the clinics where there is no psychologist or where he or she cannot see all the patients, we can train a nurse to manage pain education of patients and to have discussion regarding pain management with patients and relatives.

MC: These results that you mention are in line with another exciting study, which showed that when using the same treatment, the outcomes were better for the patients who had a careful, periodic assessment of their symptoms (4).

Coming back to the possible disadvantages of the new technologies, change with should we fear that the incidence of radio-induced cancers could be higher for intensity modulated radiation therapy (IMRT) / volumetric modulated arc therapy (VMAT)?

AGM: I tried to gather evidence to answer this question. We pooled together data from more than 2500 patients, and the incidence was significantly higher for the patients treated with IMRT/VMAT than for patients treated with 3 dimensional -Conformal Radiotherapy 3(D-CRT, in the population we studied. This does not mean that we should reject the new technologies, but this kind of information can raise awareness and change some practices for follow-up (5).

MC: We could also analyze the cases with radio-induced cancers and identify some biomarkers that increase this risk. Also, these results are significant because they raise awareness and increase the chance of detecting radio-induced cancers earlier. Of course, not only the fact that they are more frequent, but the degree of this increase in frequency matters, so, as Marie Curie said: "Now is the time to understand more, so that we may fear less."

AGM: Yes, I want that my message is correctly interpreted. There are also other data in line with our findings. I am using IMRT/VMAT/ and stereotactic body radiotherapy (SBRT), and hypofractionation, but despite the advantages of the high doses per fraction, we should not forget that there are also studies that showed a positive effect of hyper-fractionation. Very low doses, around 0.5 Gy per fraction, seem to have good results and also a chemosensitizing and immunostimulating effect (6).

MC: Should we reframe the radiobiology laws in the context of delivering high doses per fraction?

AGM: I'm not entirely sure of this. Traditionally it is not recommended to use the good old linear-quadratic model in the case of extreme hypofractionation, but some radiobiologists believe that, on the contrary, that model is still alive and well (7,8).

MC: Who should do the follow-up of the patients treated with Radiotherapy?

AGM: The answer to this question is simple in my opinion. We, the radiation oncologists, should be the ones to follow the radio-treated patients in the follow-up. In fact, we are supposed to be the most experienced clinicians in identifying and managing late complications, and in distinguishing them from other conditions, such as tumor recurrences.

MC: In this case, some colleagues might find themselves in a difficult situation. Those who see a lot of new cases - either as part of their regular work or by choice, and also have some years of practice behind, so many more follow-up cases - would have to spend more hours at work.

AGM: Honestly, I found myself in the same situation. As a result, we developed an efficient system in which we rely a lot on nurses. The patient sees the nurse first, she collects data on symptoms and current situation, and when the patient comes to me, I do not need to spend so much time to find out the news. This way I have more time to answer patients' questions. Also, the patient might share with the nurse more personal details or questions and might hesitate to address me, especially if other members of their family are present, too. However, the patient still need a discussion with the doctor, they need to ask for his/her opinion on the possibility of a cure or the risk of relapse, about what the future could bring.

MC: What is your approach regarding communication with the patients, especially when they look at the physician for the reassurance of cure, or in those situations when we are the messengers of bad news?

AGM: When I have reasons to believe that the risk of relapse is very low, I deliver an optimistic message. When the situation is severe, I tell the patients and their families that they should try to spend the remaining time in such a way that it gives it value. There are situations when family members of patients who have cancer in an advanced, incurable stage, ask me if they should try to take their dear ones to another country, where they heard there is a "special machine" that does miracles. My advice for them is to facilitate meetings with relatives, friends, or people that the patient did not see for a long time, and wishes to see or to do other small things that they enjoy, like eating a certain type of food they enjoy. Small things make a difference in the patient's life and are more important than chasing an impossible cure.

Abbreviations:

IMRT - intensity modulated radiation therapy
VMAT - volumetric modulated arc therapy
3D-CRT - 3 Dimensional-Conformal Radiotherapy
SBRT - stereotactic body radiotherapy

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