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Bridges to the Future: Precision Medicine Workshops in the 2023 Smart Diaspora Conference

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Romania is one of the European countries with the highest number of medical specialists working abroad. It is estimated that in the last decade more than 20,000 physicians chose to leave Romania for Western Europe or North America. The series of collaborative scientific conferences of Romanian diaspora launched initially in 2011, gained traction under the presidency of Klaus Iohannis who, in the fall of 2015, in order to counteract the „brain drain" exodus of highly educated professionals, encouraged the implementation of „brain regain" projects.

The 2023 edition of the conference "Smart Romanian Diaspora and Its Friends – Higher Education, Science, Innovation, and Entrepreneurship" was held in Timisoara from the 10th to the 13th of April. The event brought together several renowned experts from various academic fields, both from Romanian diaspora and from Romania, in order to discuss top trending research subjects in plenary sessions and dedicated workshops.

Personalized Medicine represented the topic of two workshops hosted by the Victor Babeș University of Medicine and Pharmacy from Timișoara. The speakers were Romanian specialists from Romania, USA, and Western Europe and the intention of these workshops was to exchange ideas and information about brand new concepts in contemporary oncology with the goal of developing research projects of mutual interest in the immediate future.

Contemporary personalized medicine has been defined broadly as „the use of combined knowledge (genetics, or otherwise) about a person to predict disease susceptibility, disease prognosis or treatment response and thereby improve that person's health" or, more restrictively, „the use of combined knowledge (genetics, or otherwise) about a person to predict disease prognosis or treatment response" or just to predict treatment response (1).

A related expression, "precision medicine" has been introduced (2) and has been used interchangeably with "personalized medicine". In the National Cancer Institute dictionary their definition is identical (3) i.e.: „a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease. In cancer, personalized medicine uses specific information about a person's tumor to help diagnose, plan treatment, find out how well treatment is working, or make a prognosis. Examples of personalized medicine include using targeted therapies to treat specific types of cancer cells, such as HER2-positive breast cancer cells, or using tumor marker testing to help diagnose cancer."

Precision medicine got a lot of attention since 2015 when Barack Obama, President of United States at that time delivered a historical speech in which he promised a significant financial to several United States research institutions in order to help implement in the near future the precision medicine paradigm in the American health care system (4).

The first workshop "Multidisciplinary Interactions at the Frontier of Personalized Medicine" was chaired by Professor Irinel Popescu, a leading expert in liver transplantation, the founder and director of the Fundeni Center for Excellence in Translational Medicine in Bucharest. The second workshop

”Personalized medicine: innovative approaches for prevention, diagnostic and treatment” was chaired by Professor Virgil Păunescu, an expert in immunology and founder and director of Oncogen Research Center in Timișoara.

We will present some highlights from the two workshops relevant to the oncology field.

The first workshop **„Multidisciplinary Interactions at the Frontier of Personalized Medicine”** was mainly focused on Gastrointestinal malignancies.

Professor Irinel Popescu opened the workshop with a presentation about the role of liquid biopsies and digital droplets polymerase chain reaction (ddPCR) for diagnostic and cancer treatment. DdPCR is a new method that improves the precision of traditional PCR by allowing more precise quantification of genetic material. Recent clinical studies have demonstrated the role of liquid biopsies for the diagnosis and management of several malignancies and the concept of minimal residual disease (MRD) has been successfully used in the treatment of colorectal cancer.

The presentation of Dr. Dan G. Duda from Massachusetts General Hospital and Associate Professor of Radiology at Harvard Medical School in Boston, US, focused on the role of the tumor microenvironment, highlighting the need for therapies that target the interaction between cancer cells and stromal components. Professor Dan G. Duda is a strong advocate of integrating basic science into clinical practice and applying to patients’ care the ‚bench-to-bedside’ concept. He emphasized the significance of genomic profiling and functional studies in identifying potential drug targets and optimizing treatment strategies in gastrointestinal (GI) malignancies.

Dr. Ovidiu Andronesi, a radiologist from Massachusetts General Hospital and Associate Professor of Radiology at Harvard Medical School in Boston, US explained how radiological biomarkers are poised to change the landscape of contemporary oncology. His research has focused on using radiomics – a field that extracts many quantitative features from standard radiological imaging data – to identify unique signatures associated with various cancer types.

Dr. Liliana Bordeianou, a GI surgeon, Chief of the Colorectal Surgery Division at Massachusetts General Hospital and Professor of Surgery at Harvard Medical School in Boston, US, discussed the role of minimally invasive surgical techniques, such as laparoscopic and robotic surgery, and emphasized their role in reducing post-operative complications, shortening recovery times, and improving overall patient outcomes.

Dr. Michael Bogdan Margineanu, a post-doctoral researcher based in London, UK, presented interesting new findings regarding the relationship between intestinal microbiota and the brain of cancer patients.

Overall, this workshop acknowledged the paradigm shifts in cancer research that highlight the growing recognition of environmental influences on cancer phenotypes, as opposed to the traditional views that placed genetics at the forefront of cancer research. It is becoming more and more clear that environmental exposures such as diet, lifestyle, radiation, pollution and even climate changes can interact with an individual's genetic background to either initiate or promote cancer growth. This new focus has highlighted the complex interplay between genes and environment, moving beyond a purely deterministic genetic perspective. By understanding how environmental factors modulate genetic risk, researchers hope to develop more personalized prevention and treatment strategies, ultimately improving cancer care and patient outcomes. This shift represents a more holistic approach to cancer research, recognizing that cancer is a multifactorial disease influenced by a combination of genetic and environmental factors.

The main topic of the first workshop, human microbiota, is of high interest in modern medicine, particularly in oncology, due to the growing understanding of its complex role in human health and disease. The trillions of microorganisms that reside in the human body have been found to significantly influence immune function, metabolism, and even the efficacy of some treatments such as chemotherapy. This understanding has prompted a shift in perspective in oncology, recognizing that microbiota may contribute to cancer development, progression, and response to treatment. Conversely, other microorganisms might exert protective effects, metabolizing potential carcinogens or modulating the immune system in a manner that suppresses tumorigenesis. Thus, the

geographical differences in microbiota, influenced by various environmental and cultural factors, can partially explain the regional disparities in cancer incidence and offer valuable insights for targeted prevention and treatment strategies. The potential to harness these microbial interactions for personalized therapies and to overcome treatment resistance has ignited extensive research and clinical interest. As a result, the study of microbiota is now seen as a frontier with the potential to revolutionize oncological care, and it has become a focal point in both translational and clinical research.

The second workshop ”**Personalized medicine: innovative approaches for prevention, diagnosis and treatment**” had a broader scope and focused on several hot topics in contemporary oncology research and practice.

Professor Virgil Păunescu presented personalized approaches in immunotherapy. First he discusussed the experience of the Oncogen Institute in producing CAR-NK cells constructs and then he introduced the concept of synthetic long peptides (SLP) vaccines for the treatment of Human Papilloma Virus (HPV) related cancers. The HPV directed SLP vaccines are particularly important for Romania where cervical cancers are much more common than in countries of Western Europe.

Professor Ștefan Constantinescu from Ludwig Institute for Cancer Research Brussels from Belgium, and University of Oxford, Oxford in UK, presented his work on signalling, epigenetic regulators, chromatin dynamics and differentiation in blood cancers and leukaemia focusing on the role of calreticulin mutants in these disorders. The molecular basis of progression over time from clonal hematopoiesis to chronic myeloproliferative neoplasms and myelodysplasia and then to secondary acute myeloid leukaemia was discussed in his presentation.

Professor Monica Neagu, Chief of the Immunology Department of the „Victor Babeș” National Institute of Pathology from Bucharest presented the key events of the transformation of a normal melanocyte into melanoma highlighting the original work of her group on the role of circulating hormones like epinephrine, norepinephrine and leptin in melanogenesis.

Professor Cristiana Tănase, Chief of the Biochemistry-Proteomics Department of the „Victor Babeș” National Institute of Pathology from Bucharest presented her original work on a set of serum biomarkers that can be used for the diagnostic, prognostic and monitoring of patients with glioblastoma.

Professor Tudor Oprea from the University of New Mexico, and Chief Executive Officer of Expert Systems based in United States, presented the role of artificial intelligence and machine learning in genome “hunting” for new targets and drug design and repurposing. His presentation had a visionary conclusion: “the natural extension of current models in medicine could lead to the development of computational reasoning tools specific to medicine (artificial intelligence in medicine - AIM) with advanced cognitive computing capabilities and data sets as complete as possible. Such platforms could mine clinical data in real time, taking advantage of -omics, biomarkers, biomedical data and electronic medical records (EMRs), providing real-time patient services”.

The current interest for personalized medicine is due on one hand to its ability to improve patient care while also making the healthcare system more efficient and more cost-productive. “The ultimate end point is the selection of a subset of patients, with a common biological basis of disease, who are most likely to benefit from a drug or other treatment, such as a particular surgical procedure. (…) Fewer side effects and lower costs are likely to result using a precision medicine approach to focus on those patients who are most likely to benefit, early in the drug development process“ (2).

The new paradigm of precision medicine involves not only a deep understanding of diseases at the molecular level potentially leading to innovative diagnostic and therapeutic methods but, also essentially, to key changes in policy and regulation that allow the rapid implementation of new diagnostic tehchniques and treatment protocols to patients.

To this end, the creation of research and innovation networks with a focus on personalized medicine represents a unique strategic opportunity to bring together stakeholders, create synergies and stimulate efforts to accelerate the evolution of healthcare towards personalized medicine.

One of the key takeaways from the workshops was the importance of multidisciplinary and transdisciplinary collaborations for achieving the goals of Personalized Medicine: **the right treatment, in the right dose, for the right patient, at the right time** (4). For this aspiration to be implemented into clinical practice, there is an urgent need for standardized, consensual methods in order to allow an efficient approach and a mutually beneficial collaboration between Romanian diaspora physicians and Romanian physicians in this rapidly evolving field. The two workshops provided a unique multidisciplinary perspective from clinicians, researchers, and experts from different fields who shared their knowledge, research data, experiences and visions for the immediate future. They presented strong evidence that integrating and harmoniously targeting various components of the cancer process may lead to better outcomes.

Such events bring us one step closer to our common purpose: a more dynamic, updated and standardized medical practice, creating bridges in the near future between US and Western Europe medicine practice and Romania. This common endeavor to find optimal strategies is part of the noble mission of adding opportunities for all patients, and improving the medical care by sharing experiences and learning from each others.

Overall, the two workshops were a unique opportunity for experts in various disciplines to exchange ideas and explore new avenues for collaboration that will hopefully shape the immediate future of Personalized Oncology in Romania and turn the „regain brain" dream of President Iohannis into reality.

Abbreviations

HER2 – human epidermal growth factor receptor 2
PCR – polymerase chain reaction
ddPCR – digital droplets polymerase chain reaction
MRD – minimal residual disease
CAR-NK – chimeric antigen receptor-transduced natural killler cells
SLP – synthetic long peptides
AIM – artificial intelligence in medicine
EMRs – electronic medical records

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The Shifting Landscape of p53abn Endometrial Cancers: A Review of the Prognostic and Predictive Impact and Current Therapeutic Directions

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Abstract

The major stepping stone laid towards the identification of high-risk endometrial cancers was made by the Cancer Genome Atlas in 2013 when the four distinct molecular subtypes were initially described. This improved risk stratification for women with endometrial cancer and ignited a major interest which led to further research on the prognostic and predictive value of molecular subtyping. Through the elaboration of ProMisE, molecular risk assignment using surrogate markers became practical and accessible to most pathology laboratories. The p53abn molecular subtype of endometrial cancer is responsible for the worst outcomes. This review aims to provide an in-depth understanding of the characteristics of these aggressive ECs, summarizing up-to-date literature regarding the prognostic and predictive implications, as well as present and future treatment directions.

Keywords: *endometrial cancer; molecular classification; p53abn; adjuvant therapy; targeted therpy*

Reviews

1. Introduction

With over 417,000 newly diagnosed cases globally in 2020, of which over 130,000 are in Europe and a reported increase in incidence rates (1), endometrial cancer (EC) is becoming a frequent cause of death by cancer in women. Going by the almost 100,000 yearly reported deaths attributed to EC (1), this type of malignancy is still facing management challenges which should not be overlooked.

Although the vast majority of ECs have a long-term favorable outcome due to early detection (80%), with 5-year survival rates as high as 95% for stage I disease (2), a major challenge in the management of early-stage EC is delineating the patients presenting with a higher risk of recurrence and in need of a more intensified therapeutic approach. Solely basing treatment recommendations on traditional clinico-pathological factors minimalizes the heterogenity of the tumoral biology and has already proven to be responsible for the frequent overtreatment or undertreatment of EC patients (3).

Paradoxically, the aggressive pathological features of a tumor can be insufficient in depicting the poorer long-term outcome for the patient with EC, as molecular characteristics have shown to be of more reliable prognosti-

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cation value. Thus, integrating high risk pathological features such as the presence of myometrial or lymphovascular invasion and a higher tumor grade can lead to a more intensified treatment approach in cases with independently excellent outcomes, such as the *POLE* mutant tumors (4). On the opposite side of the spectrum, interpreting lower-grade endometroid histotypes and early-stage diseases potentially harboring an aggressive molecular profile, such as the *TP53* mutant subtype, can lead to insufficient adjuvant treatment (3) and higher recurrence rates later on (5).

In this review, we have summarized the current literature about the importance of p53abn diagnosis as well as the prognostic and predictive implications of this aggressive subtype.

2. TCGA molecular classification and the development of ProMisE

Through an extensive and complex genome-wide investigation performed using sequencing and array testing on 373 ECs, the cancer genome atlas (TCGA) elaborated the first molecular-based stratification system of ECs (6), showing 4 subtypes, each revealing distinct prognostic and predictive clinical value: Polymerase Epsilon ultra-mutated (*POLE* ultra-mutated), microsatellite instability hypermutated (MSI hypermutated), copy number low and copy number high. While *POLE*mut ECs exhibit a highly favorable outcome, independent of other clinicopathological variables (4) and do not benefit from adjuvant therapy (7), p53abn ECs are usually associated with higher-risk histotypes such as serous, clear cell, high-grade endometroid or even carcinosarcomas (8), have a poor clinical outcome with the highest death rate documented among all molecular subtypes (5) and benefit the most from the addition of adjuvant chemotherapy.

As the technologies used in the development of the TCGA molecular classification are less likely to be widely applicable in the clinical setting due to their complexity and cost-inefficiency, Talhouk et. al developed ProMisE (9), a substantially tested classifier using a combination of IHC and mutation analysis to assign patients with EC in one of the four redefined molecular subtypes: *POLE*mut, mismatch-repair deficient (dMMR), no specific molecular profile (NSMP) and p53 abnormal (p53abn). This is more feasible and cost-effective, providing broader accessibility for most pathology labs. This classifier has proven to offer a consistent prognostic value for progression-free and disease-specific survival (10-11). In a further approach to validate the prognostic implications of the surrogate assignment, the TransPORTEC initiative analyzed 947 ECs of endometroid histology deriving from the PORTEC-1 and PORTEC-2 trials (12) and confirmed how integrating clinicopathological factors such as age, tumor grade, depth of myometrial invasion and lymphovascular space invasion with molecular alterations can additionally refine the risk prognostication of ECs. Further studies have also proven a high concordance between pre-surgical endometrial biopsy specimens and definitive hysterectomy specimens regarding the molecular subtype assignment, as well as interlaboratory concordance (13-14).

3. P53abn diagnosis and interpretation

The *TP53* mutational status, characteristic of the p53abn subtype, is most commonly determined through p53 IHC staining, which is used as a recognized surrogate for its reliable inter-laboratory reproducibility and high availability (15). This comes as a result of studies which have shown high concordance between p53abn IHC findings and *TP53* mutation obtained by NGS (16). In the analysis of the TransPORTEC cohort, the p53abn group and the presence of substantial LVSI have proven to be the strongest unfavorable indicators for locoregional and distant recurrence, as well as impaired overall survival, both being further designated as unfavorable risk factors (12). This comes as additional confirmation to another TransPORTEC study which evaluated the prognostic value of the molecular subtypes and described a lower 5-year recurrence-free survival interval (42%), a lower 5-year overall survival (40%) as well as a higher risk of developing distant metastasis in 5-years time (50%) for the p53abn subtype when compared to the other 3 molecular subtypes (17).

Table 1. p53abn important features (IHC – immunohistochemistry, NGS – next generation sequencing, RFS – recurrence free survival, EC – endometrial cancer, OS – overall survival)

p53abn subtype	
Diagnostic test	p53 IHC („null" / overexpressed pattern) NGS for TP53
Somatic copy number alterations	Very high
Defining mutation	TP53 (92%)
Clinical outcome	Poor
Prognostic value (%)	Low 5-year RFS (42%) Low 5-year OS (40%) High risk of developing distant metastasis in 5 years (50%)
Expression across EC histotypes (%)	Serous carcinomas (93%) Carcinosarcomas (85%) Clear-cell carcinomas (35%) G3 Endometroid EC (22%) G1/G2 Endometroid EC (5%)
Histological features	Lymphovascular space invasion Myometrial invasion G3

The p53abn subtype is predominantly described as having the poorest clinical outcome. Although only accounting for about 15% of all ECs, it is consistently responsible for 50 to 70% of all EC deaths (18). In a multivariable analysis, the p53abn subtype has been shown to have a 1.8x higher risk of progression than the p53 wild-type, with patients of this group also having a 2 times higher risk of death (5). This subtype is typically defined by a very high number of somatic copy number alterations and the ubiquitous *TP53* mutation. The occurrence of the *TP53* mutation with a frequency of 92% in the copy number high TCGA subtype (6) is accountable for the gain and loss of the p53 function consecutive to a vast range of mutations. While the gain of function is associated with the accumulation of nuclear p53 in the cell nucleus and is responsible for a major overexpression identifiable by IHC, the loss of function interferes with accurate protein translation and leads to the so-called „null pattern" and much more rarely to the accumulation in the cell cytoplasm (19). Singh et. al reported about a 5% prevalence of heterogenous expression patterns (15). These distinct patterns are defined by the overexpression, complete absence, cytoplasmic staining of p53 or any combination of these alternating with wild-type staining. An abnormal expression of at least 10% is required for it to be deemed as subclonal, although a more recent study proved that sub-clonality can appear as small multifocal areas in even less than 10% of the tumor volume (20). Literature suggests that the subclonal pattern might be discordant with the detection of a *TP53* mutation at times, this being dependent on the area of DNA extraction which will be later used in the sequencing process (21). A subsequent p53 expression analysis of 424 ECs included in the PORTEC-3 trial outlined a higher rate of 7% of subclonal staining, with all cases presenting as mutant overexpression and half of them presenting with an underlying *TP53* mutation (20). The subclonal *TP53* mutation is most frequently,

but not solely highlighted in *POLE* ultra-mutated or dMMR hypermutated ECs and is hypothesized as being acquired in a later stage of the tumor progression (20).

Accurately interpreting the p53 abnormal staining is detrimental in highlighting an underlying *TP53* mutation, with high pathological interobserver consistency being required. The three different staining patterns termed abnormal/mutation-type staining are: overexpression, complete absence, and cytoplasmic staining, with the latter being just recently included. In contrast, the wild-type pattern is rarely associated with the *TP53* mutation and only occurs due to less frequent truncating mutations (22). It is described as vague or diffuse staining across a variable percentage of the tumor cell nuclei in conformity with the cell's proliferative activity (22). A higher proliferation index can thus lead to more important staining and should therefore be discriminated from overexpression (22). The accumulation of p53 in the cell nucleus usually leads to visible staining in almost 100% of the cell nuclei while the complete absence of p53abn expression in the tumor cells is usually easy to recognize and shouldn't raise issues in the differential diagnosis with a p53 wild type pattern, both of them being highly indicative of the *TP53* mutant status (22). Characterized by clear cytoplasmic staining accompanied by variable nuclear staining, the cytoplasmic pattern is less commonly identified and was just recently included in the abnormal, mutated-type pattern (22). However, in the presence of strong nuclear overexpression, low-intensity cytoplasmic staining should be deemed as overexpression and not as cytoplasmic expression (22). The correct interpretation of p53abn presence via IHC optimization is majorly required to avoid underdiagnosis of ECs corresponding to a less favorable outcome.

An initially presumed impediment in the risk stratification and management of ECs based on their molecular classifier was acknowledged by the illustration of the so-called ''multiple classifiers'' (23). Based on their features, they can suggest divergent outcomes at a first glance, especially the co-occurrence of p53abn IHC in *POLE*mut or dMMR cases. The large molecular analysis of 3518 ECs done by León-Castillo et al. described their occurrence in 3% of the cases, with the most commonly recognized combinations being dMMR-p53abn (1,8%) and *POLE*mut-p53abn (0,9%), followed by the combination of these three (0,3%) (23). Although there are noticeable contrasting outcomes distinguished between multiple and single classifier ECs when comparing their 5-year recurrence-free survival rates (94,1% for P*OLE*mut-p53abn and 92,2% for dMMR-p53abn respectively) as well as distinctive clinicopathological features between the *POLE*mut and dMMR phenotypes (21), both the POLEm and dMMR signatures seem to prevail over the p53abn signature, suggesting the likelihood that *TP53* alterations in multiple classifiers occur as secondary passenger events and do not impair outcomes (23-24).

The proper risk assignment is highly important, especially in the earlier stages of the disease. Literature reviews described cases of lower-grade endometroid histotypes and early-stage diseases harboring p53 abnormalities and suggested that these patients have lower recurrence-free survival and poorer overall outcomes (25-26), predicted to be 5-fold worse when compared to another stage I low-grade disease of a different molecular subtype (27). Other studies considered the potential of decreasing the recurrence rates through the optimization of adjuvant approaches in this subset of ECs (28). However, from a more clinical standpoint, the question is raised whether over 70% of stage I-II endometrial tumors, mostly endometroid, should be analyzed for the p53abn status, as Imboden et al.'s study suggests (29) or should testing be potentially based on suggestive nuclear features, excluding unrequired testing in about half of the ECs? (30). Both these studies suggested that detection of the p53abn status was responsible only for a small percentage of patients (2,9% and 2,4% respectively) getting reassigned to a different ESGO risk group and provided limited reasoning for systematical p53abn IHC testing of all samples. In another study, discordancy between traditional clinicopathologic and molecular risk stratification was noted in a meaningful 6,6% of cases, most of them (4,5%) needing an upshift in risk grouping due to the presence of the p53abn status (31).

4. Conventional therapy for p53abn EC

According to the 2020 ESGO/ESTRO/ESP and the 2022 ESMO risk stratification system for EC, every p53abn EC with myometrial invasion should be considered high risk, independently of its histology, grade, or stage, and should therefore receive adjuvant therapy (32). p53abn expression was found to be variable across multiple histologic types of ECs, with the highest prevalence being observed in more aggressive histotypes such as serous ECs (93%), carcinosarcomas (85%), clear cell ECs (38%) and a lower prevalence in more favorable histologies (22% in grade 3 EECs and only 5% in grade 1 and 2 EECs) (8). Nevertheless, independently of the favorable or unfavorable histologic type of the tumor, the expression was associated with a worse prognosis (18), while the use of adjuvant chemotherapy showed invariable benefits among histotypes (33). As every stage I low-grade (G1/G2) endometroid EC was considered low-risk in previous stratification systems, even in the unknown unfortunate scenario of harboring the p53abn subtype, (9,7%, according to a recent analysis) (34), patients were at risk of being treated with surgery alone.

The PORTEC-3 trial is a landmark study for the current management of ECs which demonstrated the benefit of adding chemotherapy to adjuvant radiotherapy in high-risk ECs (34), but it was the publication of its retrospective molecular analysis that refined the risk groups and therapeutic strategy, as its results underlined the significant impact of combined chemoradiotherapy on 5-year RFS (58.6%) and overall survival (64.9%) in comparison with RT alone (RFS of 36.2% and OS of 41.8% respectively) in p53abn patients (35). In consonance with this study, a more recent, pan-Canadian, molecular analysis of 2472 real-world treated ECs additionally emphasized the benefit of adjuvant chemotherapy in addition to radiotherapy versus radiotherapy alone in the p53abn group, while also revealing that as much as 47% of the patients retrospectively recognized as harboring the p53abn subtype were undertreated if current guidelines where to be applied (36). Although clinicians are still reserved to use adjuvant chemotherapy for stage I ECs, both these studies also confirmed that its addition was associated with improved outcomes even for the early-stage cases bearing the p53abn subtype (35-36). In addition to their potential impact on clinical practice, these findings also serve as a considerable starting point for the development of future trials.

Table 2. Ongoing clinical trials using conventional therapies

Trial name	Start date	Estimated completion date	Phase	Inclusion criteria	Treatment plan	Primary endpoint
PORTEC 4-a NCT03469674	June 2016	Dec 2025	III	Intermediate/ High-risk	(I) Vaginal brachytherapy (II) Observation, EBRT, Brachytherapy	Vaginal recurrence at 5 years
RAINBO-RED	Nov 2021	Jan 2030	III	p53abn	p53abn-RED trial: chemoradiotherapy versus chemoradiotherapy followed by PARPi	RFS

CAN-STAMP NCT04159155	Nov 2020	Sept 2025	II/III	Early/advanced stage	Early stage: Arm A: chemotherapy Arm B1: chemoradiotherapy + chemotherapy Advanced stage: Arm C: chemotherapy Arm D1: chemotherapy + Niraparib (maintenance)	DFS at 3 years
NCT05489848	Aug 2022	Aug 2028	II/III	Post-operative stage I-IVA p53abn	(I) Radiotherapy + chemotherapy (II) Chemotherapy	2-year PFS
PROBEAT NCT05179447	Jan 2022	Dec 2023	III	p53abn	(I) Radiotherapy (II) Chemoradiotherapy	Total (vaginal, pelvic or distant) reucrrence at 3 years

** (EBRT – External beam radiotherapy, PARPi – PARP inhibitor, RFS – Recurrence free survival, DFS – Disease free survival, PFS – Progression free survival)*

Several clinical trials are currently recruiting or close to publishing results which could potentially define what's the optimal post-surgical approach for p53abn patients, furthermore refining EC treatment guidelines. The PORTEC-4a trial, which is set to publish its first results shortly, was the first to use the molecular risk profile in determining adjuvant treatment recommendations (37). Patients were randomized for observation or to receive adjuvant radiation (VBT or EBRT) based on their integrated molecular risk and compared to a standard arm receiving conventional VBT. Targeting high-risk ECs such as serous and p53abn, the randomized, phase III, CANSTAMP study is looking to evaluate the right treatment option through DFS for early-stage disease and will randomize patients to receive chemotherapy alone or a combination of CHT and EBRT, while advanced ECs are set to receive adjuvant chemotherapy alone or chemotherapy followed by PARPi maintenance (38). Additional studies are looking to assess if there are any statistical DFS differences between chemotherapy alone versus combined chemotherapy and EBRT in an attempt to avoid supplementary radiation-related toxicities and the impact of adjuvant EBRT on the time of locoregional recurrence in high-risk ECs (39-40).

5. Targeted therapy for p53abn EC

Treatment advances in p53abn ECs can also be achieved by targeting molecular alterations, with ongoing studies looking to broaden the therapeutic landscape this way in the metastatic/recurrent setting. Vast research on the complexity and aggressiveness of this subtype led to the discovery of its molecular similarities with high-grade serous ovarian (HGSOC) and basal-like breast carcinoma (BLBC) (18,41). Some of the observed resemblances with these histotypes include defects in the homologous recombination repair pathway (HRD). Studies have shown that about half of HGSOC and BLBC cases are HRD carriers (42-43). In ECs, HRD was observed in about 24% of cases, all of which were restricted to non-endometroid histologies, while an even higher prevalence of 46% was observed in the *TP53* mutated subgroup, accord-

ing to a small study (44). A more recent analysis that aimed to outline the HRD prevalence in serous ECs evaluated 19 tumors and showcased that 53% of them (10 out of 19) had an HRD score over 42, which is indicative of an HRD phenotype (45). HRD is already known to be a valuable biomarker in predicting response to platinum-based regimens in other malignancies (46-47), but not much is yet known about the benefit extent of using platinum-based chemotherapy in women with EC in the context of HRD. A recent study suggested the possibility that patients with a high HRD score could benefit from both platinum chemotherapy and the use of poly (ADP-ribose) polymerase inhibitors (PARPi) based on how tumor specimens have shown in vivo sensitivity to such therapies. On another end, the same study proved the clinical utility of the HRD score testing in predicting DFS in patients with EC, with a higher HRD score (≥ 4) being related to a worse survival compared to an HRD score <4 in the two included EC cohorts (48). With the vast majority of serous ECs expressing the unfavorable *TP53* mutation and having a clinical outcome and mutational profile rather similar to that of HGSOC, it is likely that these patients could represent an ideal candidate for further trials evaluating the use of PARPi. The rationale of using PARPi is also supported by the likelihood that a major number of p53abn ECs are harboring an HR deficiency which led to the development of multiple ongoing trials aiming to assess the effects of mono or combined PARPi therapy. The phase I/II ENDOLA trial enrolled 35 patients with recurrent/metastatic ECs and aimed to assess the safety and benefit of combining Olaparib with metronomic Cyclophosphamide and Metformin. The rationale of this combination resides in the potential of metronomic Cyclophosphamide to increase the activity of PARPi through the alkylating of DNA and the inhibition of the frequently mutated PI3K-AKT-mTor pathway with Metformin. Results have shown a mPFS of 5.1 months (7.5 months for endometroid ECs and 4.3 months for serous ECs) and an acceptable safety profile (49). PARPi maintenance therapy with Olaparib (UTOLA phase IIB trial with 53% of the patients included bearing the *TP53* mutation) (50), Rucaparib versus Placebo estimated to finish this year (51), and Niraparib (for stage III/IV serous ECs)(52) after completion of chemotherapy are also being assessed in patients with advanced or metastatic ECs sensitive to platinum regimens. In the context of recent study results suggesting a potential combined benefit of chemotherapy and PARPi in p53abn cases, the transPORTEC RAINBO trial includes a red cohort of stage I-IV p53abn ECs randomized into two arms: one receiving combined chemoradiotherapy and one receiving combined chemoradiotherapy followed by Olaparib maintenance (8).

Known to have a remarkably low abundance of TILs and a lack of TLS (53) responsible for a non-immunogenic tumor microenvironment, the p53abn subtype is a less favorable candidate for immune checkpoint inhibitor (ICI) therapy (54). Current directions are attempting to explore immune priming through the upregulation of PD-1 and PD-L1 expression by inducing DNA damage with PARPi (55), making the combination of PARPi with ICI a strategically new therapeutic option. The results of the phase II DOMEC trial which evaluated the combination of Olaparib and Durvalumab in 55 metastatic/recurrent ECs have shown an ORR of 16%, a mPFS of 3.4 months, and a mOS of 8.0 months. However, the 6-month PFS rate fell short at only 34% and did not reach the prespecified 50% (56). Another phase II trial also evaluated the combination of Pembrolizumab and Doxorubicin in patients with metastatic/ recurrent EC who received prior first-line chemotherapy and showed a mPFS of 6.4 months and mOS of 14.8 months for the p53abn subgroup (57), clearly underlining the benefit of a cytotoxic-based regimen.

The use of Cediranib, an anti-VEGF antibody, is being tested in two different trials: the three-arm, phase II, COPELIA trial and the phase II NRG-GY012 study with 6 arms in which different Cediranib-based combinations are being tested in advanced ECs (58-59). Preliminary results of the later study have shown a modest efficacy in the Cediranib plus Olaparib arm (mPFS of 5.5 months) and no major differences compared to the Cediranib monotherapy arm (mPFS of 3.8 months),

while the Olaparib monotherapy arm severly underperformed with a mPFS of just 2.0 months (59).

Other trials, some still ongoing, including the combination of Olaparib and Lurbinectedin (the POLA Study which enrolled 26 EC patients and showed a 15,4% ORR, much higher than the 6,6% observed in ovarian cancer, majorly influenced by the number of previous lines and a mOS of 4.8 months) (60), Rucaparib and Nivolumab (61) and the combination of Rucaparib and Bevacizumab in a phase II trial which has shown a modest 17% response rate for ECs but has failed to show any significant anti-tumor activity except for the patients presenting with the ARID1A mutation which showcased a higher response rate (62).

Table 3. Ongoing clinical trials using targeted therapies and immunotherapy

Trial name	Start Date	Estimated completion date	Phase	Inclusion criteria	Treatment plan	Primary endpoint
UTOLA Study NCT03745950	Feb 2019	Mar 2023	II	Advanced/ Metastatic EC	(I) Placebo (II) Olaparib	PFS1
Rucaparib vs Placebo NCT03617679	Mar 2019	May 2024	II	Metastatic/ Recurrent EC	(I) Placebo (II) Rucaparib	PFS
NCT04080284	Dec 2019	July 2024	II	Stage III/IV and platinum-sensitive recurrent USC	Niraparib	PFS at 1 year
DUO-E Study NCT04269200	May 2020	Sept 2023	III	Advanced/ Recurrent EC	(A) Chemotherapy + Placebo, followed by Placebo (B) Chemotherapy + Durvalumab, followed by Durvalumab (C) Chemotherapy + Durvalumab, followed by Durvalumab + Olaparib	PFS
NCT03660826	Sept 2018	April 2024	II	static/ Recurrent EC	(I) Cediranib (II) Olaparib (III) Cediranib + Olaparib (IV) Olaparib + Capivasertib (V) Olaparib + Durvalumab (VI) Cediranib + Durvalumab	PFS

NCT05256225	Nov 2022	Oct 2027	II/III	Stage I-IV HER2 positive Endometrial Serous Carcinoma / Carcinosarcoma	(I) Chemotherapy (II) Chemotherapy + Herceptin Hylecta (III) Chemotherapy + Phesgo	PFS OS
DESTINY PanTumor02	Aug 2020	June 2023	II	Cohort 4: HER2 positive Endometrial Cancer	Trastuzumab deruxtecan	ORR
NCT05150691	Jan 2022	June 2025	I/II	HER2 positive Endometrial Cancer	DB-1303	ORR
NCT05156268	Jan 2022	Jan 2024	II	Persistent / Recurrent EC	Pembrolizumab + Olaparib	ORR
RUBY TRIAL NCT03981796	July 2019	Nov 2026	III	Advanced (Stage 3/4) / Recurrent EC	(I) Dostarlimab + chemotherapy, followed by Dostarlimab (II) Placebo + chemotherapy, followed by Placebo (III) Dostarlimab + chemotherapy, followed by Dostarlimab + Niraparib (IV) Placebo + chemotherapy, followed by Placebo	PFS OS
AtTEND NCT03603184	Oct 2018	Nov 2023	III	Advanced / Recurrent EC	Atezolizumab + Chemotherapy Placebo + Chemotherapy	PFS OS
NCT03526432	Aug 2018	Aug 2023	II	Advanced / Persistent / Recurrent EC	Bevacizumab + Atezolizumab	CR PR
NCT03367741	April 2018	Oct 2023	II	Advanced / Recurrent / Metastatic EC	(A) Nivolumab + Cabozantinib (B) Nivolumab	PFS

** PFS – Progression free survival, EC – endometrial cancer, USC – uterine serous carcinoma, OS – overall survival, HER2 - human epidermal growth factor receptor 2, ORR – overall response rate, CR – complete response, PR – partial response*

Another common genetic abnormality identified in p53abn ECs is HER2 overexpression and/or amplification (20). In serous ECs, HER2 overexpression was reported to largely vary between 14% and 80%, while HER2 amplification was reported between 21% and

47% respectively. On the other hand, HER2 overexpression and amplification rates reported in endometroid carcinomas seem to be much lower (63). The GOG-177 study found that HER2 amplification was more commonly seen in higher-grade and serous tumors (64). Studies reporting on survival analysis of EC patients expressing HER2 amplification and/or overexpression found them to be linked to significantly shorter survivals (median of 5.2 years in HER2 overexpression and 3.5 years in HER2 amplification in all histological types) when compared to absent amplification and/or overexpression (median survival of all cases: 13 years) (65-67). When the HER2 status was retrospectively investigated in the PORTEC-3 cohort, results have shown a distinct association between HER2 positivity and the p53abn subtype, with all but one of the HER2 positive cases being classified as p53abn (95,8%). HER2 positivity was identified in 25% of all p53abn ECs, while no other subtype expressed a positive HER2 status (68). Important to note is that this analysis was not able to confirm the independent prognostic value of HER2 positivity in the multivariable analysis, but proved the relation between the positive status and a significantly worse relapse-free survival in the univariable evaluation (68). Although the initial phase II GOG study assessing the use of Trastuzumab (anti-HER2 antibody) monotherapy in HER2-positive patients with EC did not demonstrate antitumoral activity in either overexpressed or amplified cases (69), the updated OS analysis of a more recent phase II study which combined Trastuzumab with chemotherapy and compared it to chemotherapy alone in HER2 positive stage III/IV recurrent serous ECs concluded more favorable results in the experimental arm, both in terms of mPFS (17.7 months versus 9.3 months in the 1st line setting and 9.2 months versus 7.0 months in patients with recurrent disease) and mOS (29.6 months versus 24.4 months) (70).

In the randomized MITO END-2 trial, Bevacizumab combined with Carboplatin and Paclitaxel failed to demonstrate a noteworthy benefit in terms of PFS when compared to chemotherapy alone, but patients in the experimental arm experienced a significant increase in 6-month disease control rate (70.4% versus 90.7%) (71). Further analysis of the *TP53* mutational status in the GOG-86P study which combined targeted agents (Bevacizumab or Temsirolimus) with standard platinum-based chemotherapy has shown an improvement of PFS and OS in *TP53* mutant / p53abn patients that received Bevacizumab and not Temsirolimus (72), proving that the addition of Bevacizumab could be potentially beneficial in improving outcomes of p53abn ECs and establishing in it a potential biomarker value for future guidance of clinical trials (73).

The presence of the *TP53* mutation frequently leads to cell-cycle dysregulation. The tumor cell thus becomes more dependent on WEE1-mediated regulation and potentially more sensitive to the effects of WEE1 inhibition. The clinical activity of Adavosertib, a WEE1 inhibitor, was investigated in the phase IIB ADAGIO trial in 34 women with persistent or recurrent serous ECs and results have noted an ORR of 29,4%, a mPFS of 6.1 months (with 16 patients progression-free at 6 months), and a mDOR of 9.0 months (74).

In conclusion, we're currently facing a transition phase in which incorporating precise biomarkers with validated prognostic and predictive value can re-define the traditional concepts of EC management. The molecular-based risk assesment of ECs is of substantially predictive value. Therefore, applying the ProMisE classifier and further guiding treatment decissions upon results should be strongly advised for all laboratories where molecular classification using the surrogate markers is attainable. If the testing resources are limited, high-grade and high-stage cases that need adjuvant therapy should be prioritised, as this could have a great consequence on their treatment recommendations. In this day, identifying the patients most likely to have their treatment plan impacted by molecular risk-based reassignment and optimizing IHC diagnosis through consistent pathological interpretation while also avoiding unnecessary testing are some current challenges we need to overcome. Through these, we have the ability to improve outcomes where it is much needed, such as in the highly unfavourable p53abn subtype.

Abbreviations:

EC – endometrial cancer
POLE – polymerase-epsilon
TCGA – The Cancer Genome Atlas
MSI – microsatellite instability
IHC – immunohistochemistry
dMMR – deficient mismatch repair
NSMP – no specific molecular profile
NGS – next-generation sequencing
LVSI – lymphovascular space invasion
ESGO – European Society of Gynaecological Oncology
ESTRO – European Society for Radiotherapy & Oncology
ESP – European Society of Pathology
ESMO – European Society for Medical Oncology
EEC – endometroid endometrial cancer
RFS – recurrence free survival
RT – radiotherapy
OS – overall survival
VBT – vaginal brachytherapy
EBRT – external beam radiotherapy
DFS – disease-free survival
CHT – chemotherapy
PARPi – poly (ADP-ribose) polymerase inhibitor
HGSOC – high-grade serous ovarian cancer
BLBC – basal-like breast carcinoma
HRD – homologous recombination repair pathway
mPFS – median progression-free survival
TILs – tumor infiltrating lymphocites
TLS – tertiary lymphoid structures
ICI – immune checkpoint inhibitor
PD-1 – programmed death protein ligand 1
PD1 – programmed cell death protein 1
ORR – objective response rate
VEGF – vascular endothelial growth factor
HER2 – human epidermal growth factor receptor 2
mDOR – median duration of response

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Radiation Therapy for Ocular Melanoma – a Narrative Review with Insides from TRIUMF, Canada's Only Proton Beam Therapy Center

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Abstract

Ocular melanoma (OM) originates from melanocytes in the eye, predominantly in the uvea, particularly the choroid. The yearly incidence is around six cases per million. OM is not primarily driven by ultraviolet exposure like skin melanoma, but is usually caused by mutations in GNAQ or GNA11. Symptoms like blurry vision and visual field defects appear late. Diagnosis is often made via eye exams, specialized ultrasound, and rarely biopsy. This narrative review describes the radiation treatment modalities of OM and highlights the landscape of proton beam irradiation in Canada.

Historically, enucleation was the standard of care for OM. However, current strategies consider tumor size, location, patient age, visual potential, and metastatic presence. Primary treatments include radiation therapy and surgery. Radiation therapy includes plaque brachytherapy (PB), proton beam irradiation (PBI), stereotactic radiosurgery (SRS), and stereotactic radiotherapy (SRT). Surgery includes endoresection, exoresection, and enucleation. Tebentafusp-tebn has been FDA-approved for metastatic cases.

PB, the most common radiation therapy for OM, involves radioisotopes delivering radiation into the tumor. Comparable survival rates between PB and enucleation for medium choroidal melanoma have made PB the standard of care. PB has certain limitations, mainly surgical complications. PBI uses a particle accelerator for focused, high-energy proton radiation, yielding high tumor control and survival rates, though the availability of proton facilities is a significant limitation.

Vancouver is the only center in Canada for PBI, administered not in a healthcare facility but at TRIUMF (Tri-University Meson Facility). TRIUMF, the world's largest cyclotron particle accelerator, in partnership with BC Cancer and UBC Department of Ophthalmology and Eye Care Center, has treated over 200 ocular melanoma patients between 1995 and 2017, achieving a 91% tumor control rate and 82% five-year survival rate. Emerging combination therapies like Ataxia Telangiectasia Mutated (ATM) protein kinase inhibition before PBI show potential, possibly reducing radiation dose and resistance.

Keywords: *ocular oncology, plaque brachytherapy, proton beam therapy, radiation therapy, stereotactic radiosurgery, uveal melanoma, TRIUMF*

Reviews

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1. Introduction

1.1. Epidemiology

Known primarily as “skin cancer,” melanoma is a tumor arising from melanocytes located at various anatomic locations, including skin, mucosal membrane (nasal mucosa, oropharyngeal, pulmonary, gastrointestinal, vaginal, anal/rectal, urinary tract), ocular region (uvea, conjunctiva, eyelid, orbit), and rarely from unknown primary sites.

The annual incidence of eye melanoma in the United States is about six cases per one million persons (approximately 2500 new diagnoses annually) (1). Among ocular melanomas, 83% arise from the uvea, 5% from the conjunctiva, and 10% from other sites (2). The most common site for uveal melanoma is the choroid. In a study of 8033 patients with uveal melanoma by Shields et al., the tumor was located in the iris in 285 (4%), ciliary body in 492 (6%), and choroid in 7256 (90%) cases (3). Melanoma of the uveal tract is a life-threatening tumor that also jeopardizes the function of the eye. While deaths caused by the disease only account for a few cancer deaths a year, approximately one-quarter of affected patients eventually die from metastasis due to the lack of systemic treatment (1). While skin melanoma has been linked with ultraviolet exposure and harbors a *BRAF* or *NRAS* mutation, the impact of ultraviolet rays is significantly less in the development of ocular melanoma, which is usually initiated by a mutation in *GNAQ* or *GNA11* (4, 5).

1.2. Clinical presentation and diagnosis

Ocular melanoma is often asymptomatic for many years before any symptoms arise. From a clinical and practical perspective, the most common symptoms are blurry vision and visual field defects (blind spots), while in our experience, most of the other symptoms described in the literature are exceptionally rarely seen in clinical practice.

Without presenting symptoms, an optometrist or general ophthalmologist discovers most ocular melanomas via routine eye examinations. Still, an expert ocular oncologist ultimately confirms it, most often without needing a pathologic diagnosis (6). A uveal nevus is the most common simulating lesion in the differential diagnosis of uveal melanoma, and these two entities are challenging to distinguish on clinical examination. Preexisting choroidal nevi are where most choroidal melanomas are believed to arise, although few of them transform into melanoma (<1:8000) (7). Ocular examination through specialized eye ultrasound, fluorescein angiography, or optical coherence tomography (OCT) are techniques for diagnosing ocular melanoma (8). Fine needle aspiration biopsy is used with caution to avoid seeding. Still, it is necessary to confirm the diagnosis in complex cases and through genetic profiling to determine the underlying genetic abnormalities of each tumor, assessing its metastatic risk and prognosis (9).

Studies suggest that in 50% of patients, ocular melanoma will metastasize (10). The rate of metastasis varies with the anatomical location of the primary tumor within the eye, with iris melanoma having the lowest rate of metastases, as compared to ciliary bodies and choroidal melanomas (10). In patients with uveal melanoma, the clinical and histopathologic features of the primary tumor that are associated with poor prognosis include increased patient age, the largest basal diameter of the tumor, ciliary body involvement, extra scleral tumor extension, epithelioid cell type, and vasculogenic mimicry patterns (11). Patients who present with primary uveal melanoma and synchronous distant metastases are rare (less than four percent of all patients diagnosed with uveal melanoma).

1.3. Risk factors

Several risk factors, including light eyes, the Caucasian population, and certain skin conditions such as cutaneous nevi, dysplastic nevus syndrome, iris nevi, and BAP1 mutation, have been identified (1). The somatic or germline mutation of BAP1 predisposes patients to develop uveal melanoma, malignant mesothelioma, cutaneous melanomas, basal cell carcinoma, and renal cell carcinoma, requiring molecular testing and referral to hereditary cancer programs (12). A large study of iris and posterior melanomas showed a metastatic rate of 15% at 5 years and 25% at ten years (11). The most common metastasis

site is the liver (60-89%), followed by the lungs (24-29%), skin and soft tissue (11-12%), bone (8-17%), and lymph nodes (11%) (11,13). Identifying metastases prompts whole-blood genotyping testing for HLA-A*02:1, affecting therapy selection (14).

2. Results and discussion

2.1. Treatment options for ocular melanoma

Historically, the main treatment option for primary tumors in patients with ocular melanoma was enucleation. Many factors, including the size and location of the tumor, presence of extraocular extension, visual potential, patient age and preference, and presence or absence of metastases, currently guide its management, which remains a multidisciplinary challenge. Radiotherapy tends to be the preferred treatment for small and medium tumors since the Collaborative Ocular Melanoma Study (COMS) showed that survival rates between enucleation and plaque radiotherapy are comparable in patients with medium choroidal melanomas (15). At the same time, enucleation is usually performed for larger and more advanced melanomas, poor visual function, recurrent tumors, multifocal iris melanoma, and diffuse iris melanoma (13). There are currently very few treatments approved for metastatic ocular melanoma and despite the advances in the treatment of primary tumors, the rate of mortality once metastases are diagnosed is unchanged in decades (16). Several options have been reported without significant or lasting improvement, including cryotherapy, chemotherapy, and immunotherapy. Most recently, in 2022, the US Food and Drug Administration (FDA) approved tebentafusp-tebn (Kimmtrak) for the treatment of metastatic uveal melanoma or that which cannot be surgically removed, in patients with HLA_A* 02:01 (16).

2.1.1. Observation: For asymptomatic patients with small uveal melanocytic tumors (<12 mm in diameter and <2 to 3 mm in height), initial management is often observation for evidence of growth, with follow-up at two- to four-month intervals rather than immediate intervention. Imaging modalities commonly used in monitoring a small suspicious uveal melanocytic tumor include fundus photography, ultrasonography, and fundus autofluorescence to identify evidence of tumor growth, subretinal fluid, orange lipofuscin pigmentation, and other risk factors for malignant transformation (17).

2.1.2. Surgery: The main surgical procedure used for ocular melanomas is enucleation, and represented historically, the standard of care. Although eye preservation is essential and highly desirable, enucleation remains the only option for large tumors unsuitable for radiation. Indications for enucleation include large tumors with thickness >10 or 12 mm and/or a basal diameter >18 mm (18), poor visual potential and extraocular growth, proximity to the optic disc, and extensive involvement of iris, angle, or ciliary body (19).

Local resection is sometimes performed for small iris tumors only and almost never for the other anatomical locations within the eye. Tumor resection can be based either on an external approach, known as exoresection, or an ab-interno approach, known as endoresection. Even in such cases, postoperative vision is suboptimal, as an incomplete iris leaks light and vision looks distorted.

2.1.3 Radiation therapy: The current standard of care treatment for primary uveal melanoma is radiation therapy and two main types of radiation therapy exist. Since uveal melanomas are relatively radioresistant, and the eye is a closed and small space, they must be treated with high-dose focused radiation. Radiation therapy can be delivered to the eye in various ways. It can be done with a surgically implanted radioactive brachytherapy plaque containing various isotopes such as iodine-125, ruthenium-106, or palladium-103. Alternately, external beams can deliver the radiation, either in the form of charged particles such as proton or helium ions or photons, using stereotactic techniques with a Gamma knife or a Linear Accelerator.

In this review, we offer a brief and practical comparison of each technique's characteristics, advantages, disadvantages, and complications, focusing on proton beam irradiation, where we incorporate aspects learned during 22 years of treatment of ocular melanoma at TRIUMF, Canada.

3. Radiation therapy techniques used for ocular melanoma

All cells, whether normal or malignant, have some radio sensitivity secondary to two cellular factors: rapid cell division and the cell's innate ability to repair DNA damage. Ionizing radiation damages the DNA of malignant cells by causing double-strand breaks, most commonly causing the cell to misrepair (20). The extent of the damage becomes most evident during mitosis, wherein the damaged cells lose the ability to self-replicate. Another damage caused by the radiation encompasses alterations in the growth of signal transduction pathways, apoptosis, and the general regulation of the cell cycle. Cancer cells divide rapidly and often and have immature DNA repair mechanisms compared to normal cells. Melanoma has a relatively low radio sensitivity compared to many cancers but is far more radiosensitive than normal tissue (21).

A summary of radiation therapy modalities can be seen in Table 1.

Table 1: Summary comparison of radiation therapy methods

	Plaque Brachytherapy (PB)	***Stereotactic Radiosurgery (SRS)***	***Proton Beam Irradiation (PBI)***
Availability	High	High	Low
Cost	Low	Moderate	High
Indications	Small – medium, away from optic nerve	Larger (>7mm thickness), near optic nerve	Larger (>7mm thickness), near optic nerve
Complication of concern	Radiation induced glaucoma	Radiation induced glaucoma	Radiation induced glaucoma
Contraindications	Tumor close to optic nerve, large tumor thickness in comparison to base.	Tumor volume > 1/3 of globe volume	Tumor volume > 1/3 of globe volume

3.1. Plaque Brachytherapy (PB)

Plaque brachytherapy is the most common form of radiation therapy used in treating uveal melanoma worldwide and utilizes low-energy radioisotopes that constantly emit radiation photons due to radio decay, delivered through the eye wall into the tumor. Plaque radiotherapy with an apex dose of 70–100 Gy (22) is one of the most commonly used treatment modalities for posterior uveal melanoma. Initial head-to-head comparison of enucleation and PB was performed through COMS, the largest randomized controlled trial in ocular oncology, with >2,000 enrolled patients (23). The results revealed no survival differences at 5, 10, and 12 years between plaque brachytherapy and enucleation in patients with medium choroidal melanoma, making PB the treatment of choice in suitable tumors. Because the saucer-shaped plaque is sutured surgically to the sclera for the duration of treatment, very high-energy radiation is emitted near the source. There is a rapid energy loss away from the source, translating into a high degree of efficacy and little damage beyond the tumor target. Several radioisotopes have been used, including cobalt-60 (60Co), iodine-125 (125I), iridium-192 (192Ir), palladium-103 (103Pd), and ruthenium-106/rhodium-106 (106Ru/106Rh) (25). The most commonly used isotope in the United States is 125I, a gamma emitter with deeper tissue penetrance that allows for treating larger tumors. However,125I is rarely used in Europe and South America, where Ruthenium-106, a beta emitter, is most often used (although it is ineffective in large melanomas due to its lower penetrance). The choice of radioisotope is based less on their efficacies and toxicities, which are relatively similar

clinically but based on availability. Iodine-125 and palladium-103 are often used in North America due to the large repositories of these radioisotopes and the consistent supply chain. Similarly, the available quarry of ruthenium in Europe makes it the dominant radioisotope for plaque brachytherapy in Europe and South America (24). With intraoperative ultrasonography for plaque localization, the local recurrence rates, a risk factor for metastasis with plaque brachytherapy, have decreased substantially and are now similar to charged-particle radiation therapy. Consensus opinion guidelines for using radioactive plaque therapy have been published by the American Brachytherapy Society (ABS), but research is ongoing into the optimal dosimetry parameters for uveal melanoma (25). Despite comparison studies between various radioisotopes, clinically, the radioisotope is selected based on relative convenience and availability of the isotope to each treatment facility.

As PB is the standard of care for ocular melanoma, there are constant efforts to improve the technique, especially plaque placement, use of newer radioisotopes, and identification of the best optimal dose for the tumor apex, without or in combination with the inhibition of the Ataxia telangiectasia mutated (ATM) protein kinase (26). Pulverization of gold nanoparticles on the tumor before brachytherapy can absorb photons of energy, preventing the photons from passing through the tumor, and has been studied to reduce the dose of radioisotopes (27). Improvement in radiological techniques may allow for ultra-high field MRI instead of ultrasound for three-dimensional visualization of the tumor, restricted by the availability of a seven-tesla magnet required for this procedure (19). Alternatively, modern techniques, such as 3D printing of the eye and orbit, have also been studied to enhance treatment planning further (28). The main limitation for PB remains related to surgery for plaque placement. Surgical complications include double vision due to muscular injury, dry eye due to conjunctival peritomy, eyelid swelling, and the risk of anesthesia, which makes especially elderly patients poor candidates for this therapy.

3.2 Stereotactic Radiosurgery (SRS)

Stereotactic radiosurgery is an advanced type of external beam radiotherapy used mainly for larger tumors that can be visualized by CT scan or MRI, which are used to localize the tumor within the eye. The primary type of ionizing radiation utilized is photon-based (gamma or X-ray waves), characterized by slightly lower energy and increased scattering.

3.2.1 Gamma knife: A gamma knife involves immobilization within a cylindrical headpiece anchored to the patient's skull with multiple beams directed at the tumor from multiple directions simultaneously, with a potential for high amounts of radiation to be delivered at once. It appears to cause a significant slowing of the blood flow through the central retinal artery and a significant increase in vascular resistance of the smaller retinal arteries, which may explain one of its main complications: the development of therapy-related secondary glaucoma, reported as high as 47% in some series (29). Due to its multibeam ability to attack the tumor from multiple angles, several authors have also been able to de-escalate the radiation dose and still obtain an excellent killing effect.

3.2.2 Cyberknife: Like gamma knife, cyberknife is a photon-based radiotherapy that involves the external application of multiple high-intensity beams from multiple directions in rapid succession without fixation to the skull. The head is immobilized with a custom-made aquaplast mask. It offers the ability to treat larger eye tumors not amenable to brachytherapy or local resection. The availability of a cyberknife also may influence the treatment decision regarding its use, as it may be the only treatment option available in some countries (stereotactic linear particle accelerator, Slovakia). Cyberknife therapy has a higher incidence of secondary glaucoma following treatment in comparison to other standard methods of uveal melanoma radiation (30).

3.3. Proton Beam Irradiation (PBI)

Proton Beam Irradiation, an alternate method of external beam irradiation, uses heavy charged particles such as helium ions or protons. Although helium therapy was successful and showed promising results, it was discarded due to expensive operating costs. Proton beam therapy utilizes a particle accelerator to release high-energy protons from an atomic nucleus. Because of their relatively

large size, protons are not scattered within the cellular nucleus upon arrival at the target cell. This allows for a much-focused beam of radiation with minimal effect on the tissue surrounding the tumor. Protons also have the advantage of undergoing a rapid reduction of energy upon arrival at their target, known as the Bragg effect, which implies that high-energy protons will stop at their target, cause damage to their target, and not pass through the target to cause an effect on tissue past the tumor (normal tissue). Protons are thus able to cause more DNA damage with less total radiation energy.

PBI is an effective and safe treatment for ocular melanoma, with excellent local tumor control >90% and a 5-year overall survival of 70-85% (31, 32). PBI could be preferred to brachytherapy for tumors with a location that may challenge plaque positioning or have a risk of suboptimal immobilization of the plaque (for instance, posterior pole), in the treatment of larger tumors with a height of more than 5 mm, or tumors with a narrow base (32) The main limitation of PBI is the availability of protons and the facilities that produce them. Developing a proton accelerator is cumbersome and extremely expensive, and PBI is available only in a few centers worldwide (19). For decades, there were only two in the United States (Boston and California) and a few in Europe, making treatment for most patients impractical. Second, successful proton therapy of an eye requires placing a radiopaque target on the eye's surface to aim the proton beam, which requires a surgical procedure ahead of treatment, typically under general anesthesia. However, the placement of tantalum markers used to mark the tumor and safety margins is surgically easier than plaque placement, and computer adjustments are possible after insertion. Third, the proton accelerator is external to the eye, which is a highly mobile organ. Because the beam is very focused, there is a real possibility of missing the target tumor with consequent treatment failure. Despite the limitations, continuous development can improve the technique to achieve better outcomes (33).

At the beginning of 2023, 89 proton therapy centers operated worldwide and 41 in the United States (34). Vancouver remains the only center in Canada for PBI, administered not in a healthcare facility but at TRIUMF (TRI-UNIVERSITY MESON FACILITY), the world's largest cyclotron particle accelerator (520Mev, 18-meter-long diameter vacuum tank). Between 1995 and 2017, one of TRIUMF's beamlines used for cutting-edge research in nuclear physics was also used for cancer treatment of ocular melanoma at the Proton Therapy Research Center, where in conjunction with BC Cancer and the UBC Department of Ophthalmology and Eye Care Center, more than 200 patients were treated, many under the direct care of one of the authors (Dr. Ma). Approximately 40 patients with eye melanoma were diagnosed locally, and a quarter of them underwent PBI at TRIUMF, while the remaining had brachytherapy. Patients aged 14 to 86 had customized equipment to ensure their treatment's comfort and safety. The painless treatment lasted 90 seconds and was administered four times over four days, similar to protocols used by other centers (35). Local tumor control was 91% effective, with a five-year survival rate of 82%, with the affected eye saved in 80% of cases (32). The local experience confirmed the importance of PB and PBI radiation treatments, which were considered complementary for achieving the best outcomes and required personalized treatment from multidisciplinary treatment selection to implementation and follow-up. Figures 1-4 depict the facilities and patient set-up for administering this therapy, and figure 5 the pathology of an ocular melanoma treated by enucleation in Vancouver.

For the treatment of larger tumors and tumors close to the optic nerve, plaque brachytherapy is not used. Instead, SRS or PBI has been used for many years as alternatives to enucleation. While SRS has been demonstrated to have higher rates of post-treatment glaucoma, vitreous hemorrhage, and significant visual loss, overall rates of eye retention and survival are similar between SRS and PBI (36, 37). PBI remains the less accessible option of the two due to its prohibitive cost.

Among the most exciting combination therapies is inhibiting ATM protein kinase before radiation therapy to reduce the required radiation dose. PBI may be the first to incorporate ATM inhibition and decrease the ocular melanoma relative resistance before initiating PBI.

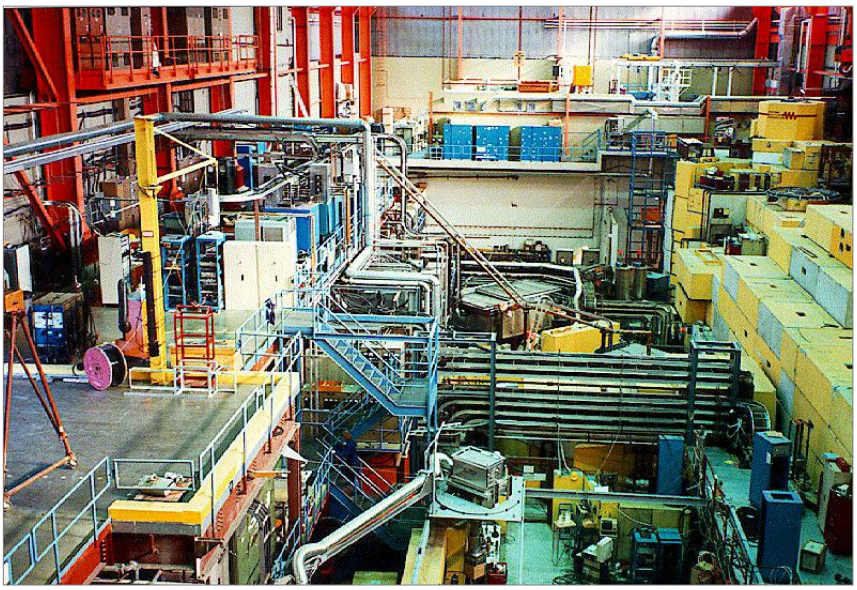


Figure 1: TRIUMF: The only Canadian Center for Proton Beam Therapy Treatments: Ocular Melanoma Treatments From 1995 to 2017: Not a Hospital Facility

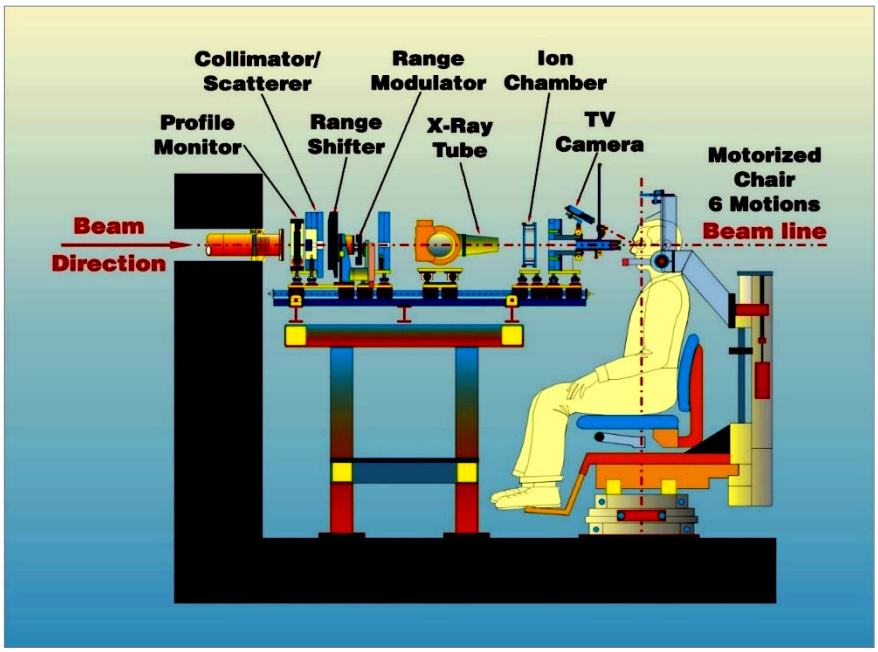
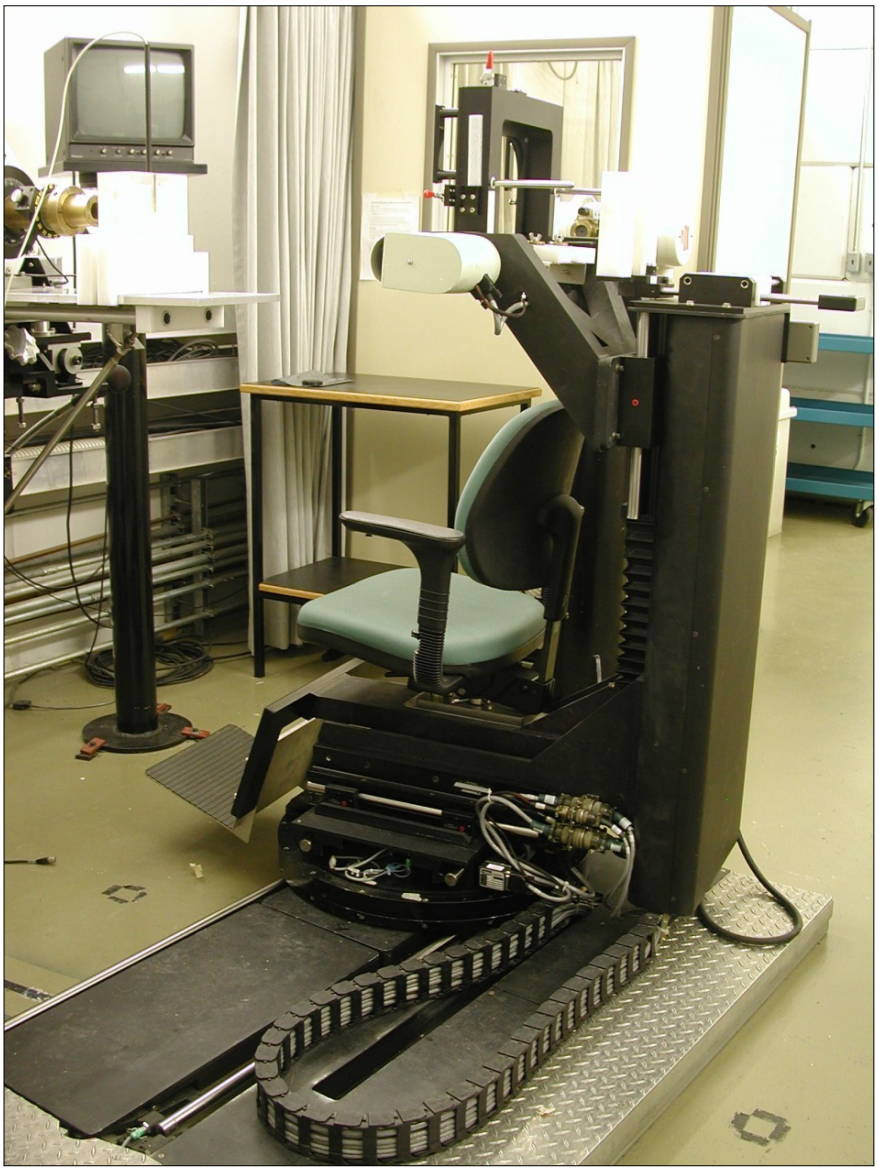
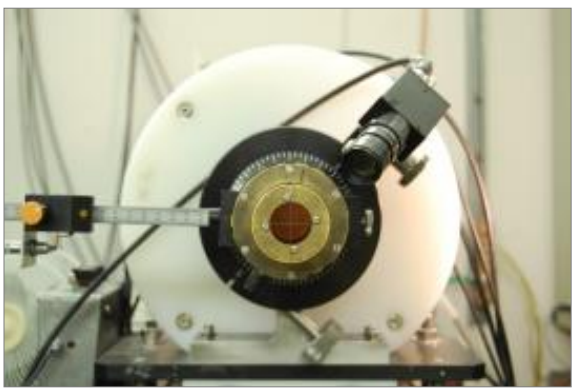


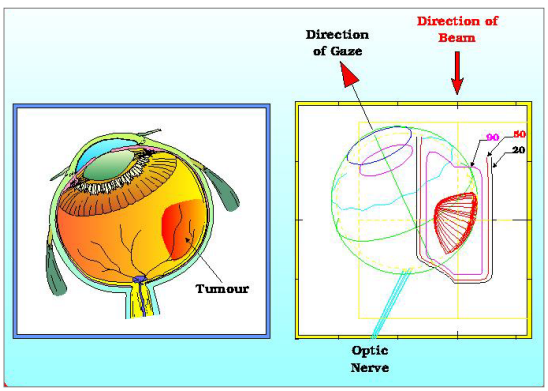
Figure 2: The Beam Preparation and Patient Equipment at TRIUMF, Canada
The proton beam is centered using a profile monitor onto a collimator scatterer, which has a .8 mm Pb foil that uniformly spreads out the beam over about 30 mm diameter. The range shifter and range modulator are placed near the scatterer. The dose is measured using an air ion chamber and the patient is seated in a chair with 6 degrees of freedom.

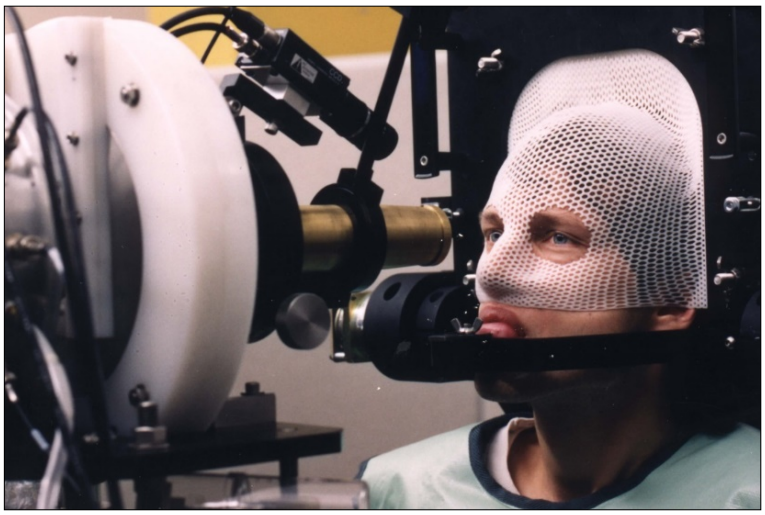
Figure 3: Treatment Set Up and Patient Treatment at TRIUMF, Vancouver, Canada



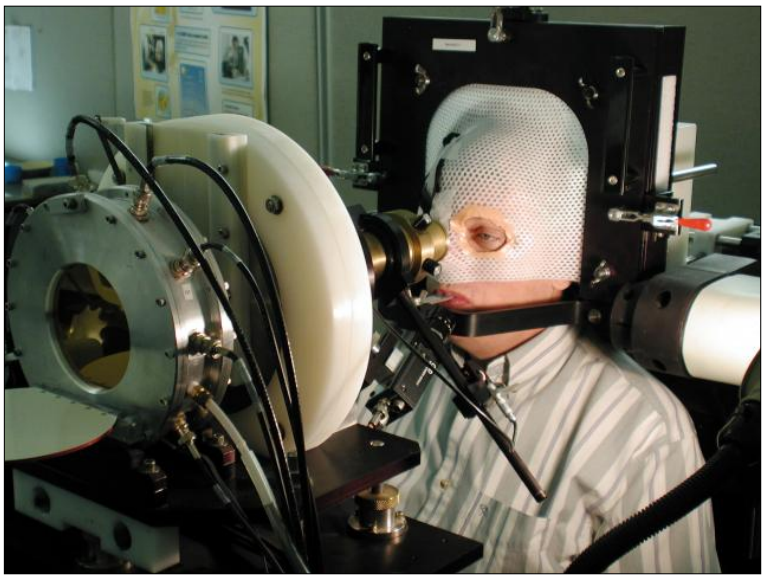
Patient Chair and Set-Up for Treatment: The chair has six degrees of freedom and can be rotated around a vertical axis, typically plus/minus 15 degrees to assist the positioning of the patient







Before Initiation of Treatment: multiple gaze angles are assessed, and the most optimal azimuthal and polar angles are chosen to treat the tumor, but spare anterior chamber, optic nerve, and lacrimal gland.



Patient in Treatment Position
(treatment time approximately 1 minute, $50Gy_{pr}$ in 4# in 4 days)

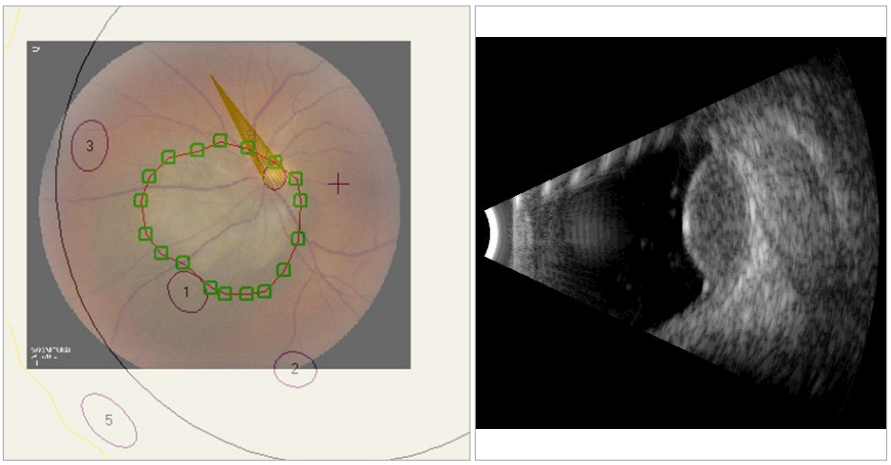


Figure 4. Treatment Planning: The tumor is drawn onto the globe using EYEPLAN software, aided by ultrasound photographs of the fundus.

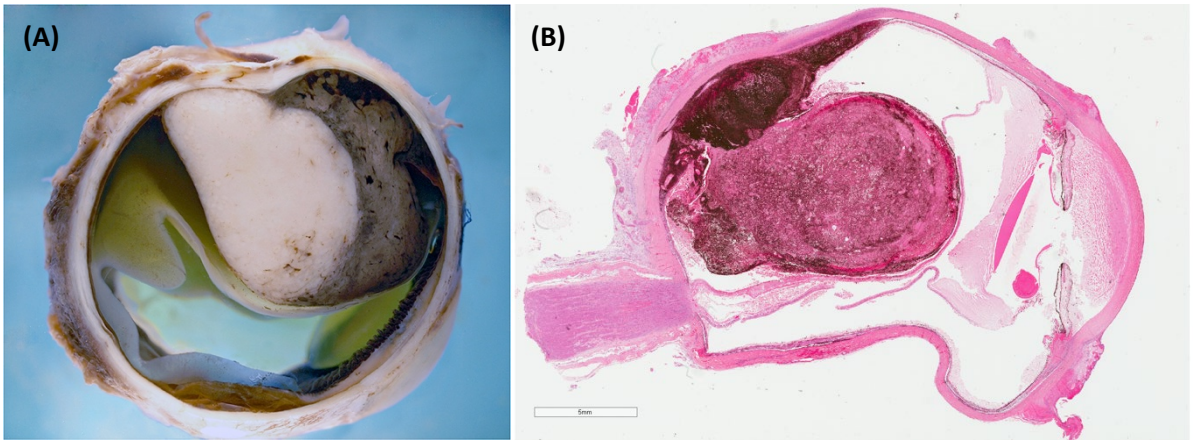


Figure 5: Ocular Melanoma: (A) macroscopic and (B) microscopic view from an enucleation procedure. (Courtesy of Dr. Rasmussen, Ophthalmologic Pathologist, Vancouver General Hospital).

4. Conclusion

OM remains a rare disease with treatment specific to its unusual location. Therefore, it may be one type of cancer many oncologists may never directly encounter. For those, as well as for acknowledging the dedication, work, and results of the Canadian group at BC Cancer and TRIUMF, we decided to write this narrative review, which may spark the readers' curiosity to look for future reads on the topics of OM or PBI.

Abbreviations:
BRAF – v-Raf Murine Sarcoma Viral Oncogene Homolog B
NRAS – Neuroblastoma RAS Viral Oncogene Homolog
GNAQ – Guanine Nucleotide Binding Protein (G Protein), Q Polypeptide
GNA11 – Guanine Nucleotide Binding Protein (G Protein), Alpha 11
OCT – Optical Coherence Tomography
BAP1 – BRCA1 Associated Protein-1
HLA-A02-1 – Human Leukocyte Antigen A02-1
COMS – Collaborative Ocular Melanoma Study
FDA – Food and Drug Administration
TRIUMF – Tri-University Meson Facility
PB – Plaque Brachytherapy
Gy – Gray (unit of ionizing radiation dose)
ABS – American Brachytherapy Society
ATM – Ataxia Telangiectasia Mutated
MRI – Magnetic Resonance Imaging
PBI – Proton Beam Irradiation
PBT – Proton Beam Therapy
CT – Computed Tomography
UBC – University of British Columbia
MeV – Mega Electron Volt

Statements:
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The Role of Subventricular Zone Irradiation in High-Grade Gliomas – a Narrative Review

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Abstract

High-grade gliomas (HGGs) are aggressive brain tumours associated with poor prognosis and treatment outcomes. Novel therapeutic strategies are urgently needed to improve patient outcomes. One approach currently under investigation is targeting the subventricular zone (SVZ), a specialized region of neural stem and progenitor cells in the adult brain. This review explores the role of the SVZ in gliomagenesis and examines preclinical and clinical studies investigating the effects of SVZ irradiation in HGGs. The potential mechanisms underlying the efficacy of SVZ irradiation are discussed, and the clinical relevance of SVZ in HGGs is highlighted. Retrospective studies examining the relationship between SVZ irradiation and survival metrics have yielded mixed results, with some studies favouring targeting the SVZ and others not. Prospective studies have also shown conflicting findings. The debate over whether to irradiate or spare the SVZ continues, considering the potential impact on cognitive function and survival outcomes. This review provides insights into the current understanding of the SVZ as a potential therapeutic target in HGGs and outlines future directions for research and clinical translation.

Keywords: *glioma, radiotherapy, subventricular zone, glioblastoma, survival*

Reviews

2. Introduction

High-grade gliomas (HGGs) are a group of aggressive malignant brain tumours with dismal prognosis and treatment outcomes. According to the World Health Organization 2021 classification, adult-type HGGs include IDH mutant gliomas (oligodendrogliomas grade 3, astrocytomas grade 3, astrocytomas grade 4) and IDH wild-type glioblastoma (GBM) (1,2). These tumours are characterized by cellular atypia, increased mitotic activity, vascular proliferation and necrosis, making them highly invasive and resistant to conventional treatment modalities, which include surgery whenever it is possible, followed by radiotherapy and/or chemotherapy.

Among HGGs, GBM is the most common and aggressive primary brain tumour in adults (3). Standard treatment for newly diagnosed GBM consists of maximal safe resection followed by radiation therapy and concurrent and adjuvant temozolomide (4,5).Tumour Treating Fields is a new therapeutic strategy

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that can also be added to the maintenance therapy, as it had been shown to prolong overall survival (OS)(6).

Despite all the therapeutic efforts, the median OS for newly diagnosed GBM is 8-15 months, while for recurrent GBM it is 6-9 months (7). Hence, it is of utmost importance to find novel therapeutic strategies to improve treatment outcomes.

One approach currently under investigation is targeting the subventricular zone (SVZ), a specialized region of neural stem and progenitor cells in the adult brain.

In this review, we discussed the role of the SVZ in gliomagenesis and preclinical and clinical studies investigating the effects of SVZ irradiation, highlighting the potential mechanisms underlying its efficacy. Finally, we also discussed future directions for research and clinical translation.

3. Role of the SVZ in gliomagenesis

Over the last decade, it emerged that within the brain there are zones of neural stem cells (NSCs), multipotent cells that have the ability to self-renew and differentiate into neurons, astrocytes, and oligodendrocytes. They play a crucial role in brain development from the embryonic stage throughout adulthood by generating new neurons and glial cells, being increasingly considered an important source of neuronal plasticity(8).

NSCs are primarily found in two regions of the adult brain: the SVZ of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus. The SVZ were shown to play a role in tissue repair and prevention of neurodegenerative diseases, while the SGZ generates NSCs that are involved in pathways of learning and memory (8).

However, studies also revealed intriguing connections between the NSCs and HGGs. Glioma cells were shown to originate from these zones, where they exhibit a remarkable ability to migrate along the specialized pathways provided by these neurogenic niches (9).

The SVZ is the major site of neurogenesis in the brain and the richest zone in NSCs. Research showed that NSCs in the SVZ share similar molecular profiles and several distinctive characteristics to proliferative glioblastoma stem cells (GSCs), suggesting that NSCs are potential initiators of gliomagenesis and are responsible for the aggressive behaviour of this disease (10,11,12). Moreover, the SVZ was hypothesized to be implicated in tumour recurrence, as delocalized residual GSCs can further maintain a malignant state even after extensive surgical resection and standard treatment approaches. These findings highlight the importance of understanding the role of the SVZ in HGGs and exploring its potential as a therapeutic target.

4. Clinical relevance of the SVZ

The anatomical contact with the SVZ gained significant attention in the context of HGGs. The first evidence that underlines the negative impact of the SVZ on the treatment outcomes came from a retrospective clinical study describing that a GBM directly in contact with the SVZ on the preoperative MRI has a more invasive character and was associated with multifocal disease in adults(13). The authors also delineated four distinct patterns that provided a comprehensive characterization of the involvement of the SVZ: GBM in contact with the SVZ and the cortex, GBM invading just the cortex, GBM invading just the SVZ and GBM invading neither structure. They concluded that anatomical contact of the tumour with the SVZ correlates with lower survival rates in GBM. This was further confirmed by Mistry et al in a meta-analysis(14) where contact with the SVZ was found to be an independent negative prognostic factor.

5. Rationale for considering the SVZ during radiotherapy planning

There are several potential treatments that target the SVZ in HGGs. One such treatment is irradiating the SVZ, which may improve outcomes by directly targeting this putative sanctuary site. Irradiation of the SVZ holds the potential in reducing tumour-initiating cells, disrupting the tumour microenvironment, and improving treatment response. Considering their role in glioma growth, targeting these cells may slow GBM growth and potentially improve survival outcomes. Contradictory, irradiating

these sites could also damage the auto-repair capacity of the human brain and lead to greater cognitive deficits and poorer survival outcomes. As a consequence, there is a continuous debate over whether irradiating or sparing the SVZ is more beneficial for patients with HGGs.

The hypothesis that manipulating the irradiation doses on the NSC niches was also applied to the treatment of brain metastasis. Traditional treatment approaches such as whole-brain radiation therapy (WBRT) were associated with cognitive decline and neurocognitive deficits, which can significantly impact the quality of life of these patients. Recognizing the importance of preserving NSC function, researchers explored novel techniques to spare these essential cells while targeting metastatic lesions (15). Current research is exploring the feasibility of selectively sparing these NSC compartments during WBRT and prophylactic cranial irradiation for brain metastases (16) and of avoiding the hippocampus during WBRT (17).

6. Review of the retrospective studies

There are already numerous studies that evaluated the hypothesis that irradiating the SVZ can have a role in slowing HGG growth and decreasing its recurrence rate. They examined the relationship between the incidental radiation dose to the SVZs delivered during the radiotherapy sequence and survival in HGG patients.

The methodology of these studies was similar: dividing the patient cohort into low and high SVZ dose groups and comparing the doses with survival metrics, such as OS and progression-free survival (PFS).

We summarized the findings of these studies in Table 1 and 2.

6.1 Studies favoring targeting the SVZ

Evers et al.(18) retrospectively evaluated for the first time 55 patients with HGGs in a study where the high-dose group included patients who received a mean dose of 43 Gy or higher to the bilateral SVZ (biSVZ) region. This value represented the median mean dose in the biSVZ across the entire cohort. The results indicated that the high-dose group showed a significant improvement in PFS (15 vs 17.2 months P=0.028). It is worth noting that no correlation was found between the incidental dose to the hippocampus and PFS, suggesting that irradiation of other neurogenic niches in the brain does not provide any benefit.

Gupta et al.(19) analysed a group of 40 GBM patients, divided based on the median dose to the ipsilateral SVZ (iSVZ) of 59.9 Gy. The study demonstrated that the mean dose to the ipsilateral SVZ was an independent predictive factor for improved OS (HR = 0.87, 95% CI 0.77-0.98; P = 0.025), but not for PFS. In this patient cohort, high radiation doses (>57.9 Gy) to the contralateral SVZ (cSVZ) were associated with a decrease in PFS (P=0.02) and OS (P=0.05).

Lee et al.(20) analysed a larger cohort of 173 GBM patients in a similar manner. Instead of using the median iSVZ dose to divide the patients, they decided that a higher radiation dose would be warranted to induce the death of GSCs and applied a threshold of 59.4 Gy. The results of the study showed that a high iSVZ dose significantly correlated with longer PFS (12.6 vs 9.9 months, P=0.042) and remained significant in the multivariate analysis (P=0.009; HR=0.45, 95% CI=0.25-0.82). A high dose of radiation to the SVZ was also correlated with improved OS, but this correlation was not significant (25.8 vs 19.2 months, P=0.173). These data were reanalysed using different threshold values, including the threshold value used by the first group of researchers of 43 Gy for the biSVZ, as well as 50 and 55 Gy for the iSVZ, but the analysis following the establishment of these threshold values did not result in significant differences in PFS and OS.

Chen et al. (21) similarly evaluated 116 GBM patients. Among patients who received a high iSVZ mean dose (>40 Gy), no significant difference in OS and PFS was observed compared to the group of patients who received a lower dose. It is important to note that among the 41 patients who underwent gross total resection (GTR), those who received a high dose of radiation to the iSVZ had a significant increase in PFS (15.1 vs 10.3 months, P=0.028) and OS (17.5 vs 15.6 months, P=0.027).

In a more recent abstract, Ravind et al.(22) conducted a retrospective analysis of 50 GBM

patients and reported that in the group of patients who received a mean dose of over 50 Gy to the iSVZ, OS was higher (19.83 vs 6.07 months, P=0.031), while cSVZ doses over 37 Gy were associated with an improvement in OS, although not significant (19.83 vs 8.73 months, P=0.118).

A study by Foro et al.(23) on 65 GBM patients was the only one to find an improvement in PFS in patients who received a cSVZ dose higher than 48.8 Gy (75th percentile) (HR 0.46; 95% CI=0.23-0.91 P=0.028), but no association with OS.

In a retrospective study evaluating a dose-escalated radiotherapy regime in a group of 72 GBM patients, Kusumawidjaja et al.(24) found an association between a higher iSVZ and an improvement in PFS (HR=0.95; CI=0.9-1; P=0.052). Furthermore, patients who received 50 Gy to the entire SVZ volume had a better PFS (HR =0.52; 95% CI =0.27–1.02; P=0.055).

The most recent evidence comes from Ermis et al (25), who demonstrated that an iSVZ dose ≥ 50 Gy was correlated with better PFS (8 vs 6 months; P < 0.001) and OS (16 vs 11 months; p < 0.001). Lower doses to the contralateral SVZ (<32 Gy) were also associated with improved PFS (8 vs 6 months; P=0.03) and OS (15 vs 11 months; P=0.001).

Table 1. Retrospective studies favouring irradiation of the SVZ

First author Year reference	Number of patients	Tumor type	High dose group (Dmean)	PFS (high vs low dose group)	OS (high vs low dose group)
Evers 2010 (18)	55	Gliomas grades III and IV	biSVZ > 43 Gy	15 vs 7.2 months (p=0.028)	NA
Gupta 2012 (19)	40	GBM	iSVZ > 59.9 Gy cSVZ > 57.9 Gy	10 vs 11 months (p=0.92) 10 vs NR (p=0.02)	17 vs 15 months (p=0.95) 14 vs NR (p=0.05)
Lee 2013 (20)	173	GBM	iSVZ > 59.4 Gy	12.6 vs 9.9 months (p=0.042)	25.8 vs 19.2 months (p=0.173)
Chen 2013 (21)	116 (41 with GTR)	GBM	iSVZ > 40 Gy	GTR only: 15.1 vs 10.3 months (p=0.028)	GTR only: 17.5 vs 15.6 months (p=0.027)
Ravind 2015 (22)	50	GBM	iSVZ > 50 Gy		19.83 vs 6.07 months (p=0.031)
			cSVZ > 37 Gy		19.83 vs 9.73 months (p=0.118)
Foro 2015 (23)	65	GBM	cSVZ > 48.8 Gy		15.5 vs 11.9 months (p=0.028)
Ermis 2023 (25)	147	GBM	iSVZ > 50 Gy cSVZ > 32 Gy	8 vs 6 months (p<0.001) 6 vs 8 months (p=0.03)	16 vs 11 months (p<0001) 11 vs 15 months (p=0.001)

** Dmean – mean dose, PFS – progression-free survival, OS – overall survival, GBM – Glioblastoma, GTR – gross total ressection, NA – not available, NR – not reached, biSVZ – bilateral subventricular zone, cSVZ – contralateral subventricular zone, iSVZ – ipsilateral subventricular zone*

5.2. Studies not favoring targeting the SVZ

Slotman et al.(26) attempted to replicate the findings of Evers et al. in a cohort of 40 GBM patients. The threshold used to separate the cohort into a high-dose and a low-dose radiation group was also set at 43 Gy. The study did not find any correlation between the doses to the bilateral, ipsilateral, or contralateral SVZ and PFS or OS. However, they did observe a correlation between the low dose to the contralateral SVZ and an increased number of distant recurrences (outside the radiation field).

A subsequent study conducted by Elicin et al.(27) suggested that the correlation between the SVZ dose and survival outcomes is much more complex. The cohort of 60 patients was analysed using different threshold values for the iSVZ and cSVZ doses, based on the 25th, 50th, and 75th percentiles. Univariate analysis showed that a higher dose of 59.2 Gy (75^{th} percentile) to the cSVZ is a negative prognostic factor for PFS (7.1 vs 10.3 months, P=0.009), but this effect lost its statistical significance in the multivariate analysis. In the subgroup with subtotal resection or biopsy only, the same cSVZ dose was a negative prognostic factor for OS (HR: 4.83 [95% CI 1.71–13.97], p = 0.004). Similarly, an iSVZ dose above 62.25 Gy (75^{th} percentile) was correlated with a decrease in PFS in the subgroups of patients with a KPS > 90 (HR: 2.58 [95% CI 1.03–6.05], p = 0.044) and those with tumours not invading the SVZ (HR: 10.57 [95% CI 2.04–49], p = 0.008). Although this result could be explained by the effects of a large tumour mass, there were no correlations found between the clinical target volume (CTV) and PFS or OS in both univariate and multivariate analyses.

Sakuramachi et al.(28) studied a cohort of 74 glioma patients and found that high iSVZ radiation doses did not affect PFS or OS. In the subgroup of 58 GBM patients, an iSVZ dose higher than 58.2 Gy was correlated with a reduced PFS, without any significant effect on OS.

In the largest retrospective study to this date, including 370 GBM patients, Murchison et al.(29) did not find any correlation between iSVZ, cSVZ, biSVZ doses and PFS or OS. Even more recently, in a retrospective analysis of 95 patients diagnosed with anaplastic gliomas, Valiyaveettil et al.(30) also found no significant association between the dose delivered to the SVZ and PFS or OS.

In 2022, Bruil et al.(31) conducted a study on 226 HGG patients, which also included an evaluation of the ipsilateral SGZ (iSGZ) doses. In their analysis an iSVZ dose greater than 30.33 Gy was correlated with a lower median OS (10.7 vs 14 months, P=0.011) and an iSGZ dose greater than 29.11 Gy was also associated with a lower median OS (10.7 vs 15.5 months, P<0.001), further underscoring a potential role for sparing the iSVZ and iSGZ during radiotherapy.

Table 2. Retrospective studies not favouring the irradiation of the SVZ

First author Year reference	Number of patients	Tumor histologies	High dose group (Dmean)	PFS (high vs low dose group)	OS (high vs low dose group)
Slotman 2011 (26)	40	GBM	iSVZ, cSVZ, biSVZ > 43Gy	No correlation	No correlation
Elicin 2014 (27)	60	GBM	cSVZ > 59.2 Gy	7.1 vs 10.3 months (p=0.009) No correlation in multivariate analysis	
Sakuramachi 2015 (28)	74	HGG	iSVZ > 58.2 Gy	No correlation	No correlation

Murchison 2018 (29)	370	GBM	iSVZ > 40, 49, 59.4 Gy cSVZ > 28.1, 40, 59.4 Gy biSVZ > 40, 40.8, 59.4 Gy	No correlation	No correlation
Valiyaveettil 2019 (30)	95	Gliomas grade III	iSVZ > 54 Gy	Decreased in univariate analysis No correlation in multivariate analysis	
Valiyaveettil 2020 (33)*	74	GBM	iSVZ > 58 Gy	11 vs 12 (p=0.34)	13 vs 13 months (p=0.27)
Bruil 2022 (31)	226	HGG	iSVZ > 30.33 Gy		10.7 vs 14.0 months (P = .011)

* prospective study

Dmean – mean dose, PFS – progression-free survival, OS – overall survival, GBM – Glioblastoma, HGG – high-grade glioma, biSVZ – bilateral subventricular zone, cSVZ – contralateral subventricular zone, iSVZ – ipsilateral subventricular zone

6. Review of the prospective studies

In an originally planned prospective study to evaluate the effectiveness of hypofractionated high-dose IMRT for newly diagnosed GBM(32), the researchers observed improved OS outcomes specifically in cases of radionecrosis occurring in the SVZ (36.2 vs 13.3 months, P=0.0001), but also significant decrease in Karnofsky Performance Status in long-term survivors. Radionecrosis surrounding the tumour site was also correlated with better survival outcomes, but this correlation did not reach statistical significance.

The first prospective clinical study investigating the irradiation of NSC niches in GBM was conducted on 74 patients who underwent total surgical resection followed by radiotherapy and chemotherapy (33). The CTV included the ipsilateral periventricular zone (PVZ), defined as a 5 mm expansion all around the lateral ventricles, and it included the SVZ, defined as a 5 mm lateral expansion of the lateral ventricles. The mean doses for the iSVZ and biPVZ were 55.1 Gy and 56.2 Gy, respectively, and the median OS for the entire group was 13 months. The group was dichotomized according to the median SVZ and PVZ doses and the results did not show a correlation between OS and PFS and the doses delivered to the iPVZ, cPVZ, bPVZ iSVZ or cSVZ, bPVZ.

7. Discussion

Comparing these studies can be challenging due to their retrospective nature and the fact that they do not control for important variables such as patient selection, radiation dose, threshold values, and treatment planning strategies. Additionally, classical prognostic factors like O6-methylguanine DNA methyl transferase (MGMT) or isocitrate dehydrogenase (IDH) status were often disregarded.

There is also room for improvement in determining the value of survival metrics, as PFS and OS were not collected in all the studies. Considering the lethality of GBM, OS is the most reliable parameter for assessing treatment efficacy, and the value of PFS should be reflected in OS since disease recurrences do not extend beyond the central nervous system (34). However, evaluating OS, in this case, can be ambiguous and challenging due to the effect of salvage therapy administered to patients at the time of progression or recurrence of the disease. Salvage therapy options include surgical reintervention, reirradiation, TMZ, lomustine (CNNU) and

bevacizumab, but at the moment there is no consensus for selecting it (2,35,36).

The relationship between the neurogenic niches and the CNS tumours remains a complex one, which also deserves a more detailed study of the hippocampus and the neurocognitive functions. Routinely assessing cognitive impairment could also provide clues for further treatment optimization.

A recent preclinical study was conducted to identify whether the tumour microenvironment in the brain influences the response of GSCs to radiation therapy (37). It showed that GSCs that migrated to the olfactory bulb are more radioresistant than those that migrated to the corpus callosum or the striatum. Therefore, the olfactory bulb also harbors a niche of radioresistant GSCs, and correlating radiation doses at the olfactory bulb with survival outcomes would also be worth studying.

In the studies considered in this review, there is significant variation in the delineation of the SVZ. It can be assumed that it cannot be accurately and uniformly done due to the significant variability in shape and volume of the lateral ventricles among patients and between the simulation CT and MR images. This becomes challenging when the tumour invades the entire thickness of the lateral ventricle. When the lateral ventricle is not visible, it is difficult to determine if the tumour invaded it, and whether the ipsilateral SVZ can be considered symmetrical to the contralateral one, or if the lateral ventricle is compressed and located in the immediate vicinity of the midline of the cerebral hemispheres, in which case the SVZs are no longer symmetrical.

There has been no guideline regarding the anatomical delineation of the SVZ until 2022, when Bruil et al. (31) provided along with their study a SVZ atlas, including its subregions, where the thickness of the zone is only 3 mm, significantly smaller than what others considered before. A subregion analysis would also be critical as the SVZ was demonstrated to be a highly heterogeneous zone. The atlas is openly available, which enables reproducibility and makes further assessments of the doses to the SVZ and its subregions easier.

The evaluation of the benefit-risk balance specific to targeting the SVZ in children has not been conducted yet and requires further investigation.

A randomized phase II clinical study is underway that examines PFS in patients with newly diagnosed GBM treated with a radiation treatment plan that intentionally prescribes 60 Gy to the iSVZ compared to a standard radiotherapy regimen (NCT02177578)(38).

8. Conclusions

The potential benefits and risks of targeting the SVZ in adult patients were examined in numerous studies so far. However, a definitive conclusion cannot be drawn based on the current literature review. We still need other prospective and randomized studies to establish which type of patients may benefit from the irradiation or avoidance of the SVZ and what are its subregions worth considering during radiotherapy delivery.

Abbreviations:

biSVZ – bilateral subventricular zone
cSVZ – contralateral subventricular zone
GBM – glioblastoma
GTR – gross total resection
GSC – glioblastoma stem cell
HGG – high-grade glioma
iSGZ – ipsilateral subgranular zone
iSVZ – ipsilateral subventricular zone
NSC – neural stem cells
OS – overall survival

PFS – progression-free survival
SGZ – subgranular zone
SVZ – subventricular zone
WBRT - whole-brain radiation therapy
NA - not available
NR – not reached

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Genetic Alterations in Glioblastoma and Their Clinical Implications – A Comprehensive Review

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Abstract

Glioblastoma (GBM) is the most aggressive primary brain tumor with limited treatment options and poor prognosis. In recent years, molecular research has provided valuable insights into the underlying mechanisms of GBM, uncovering key molecular alterations and signaling pathways that drive tumor development and progression. Driver mutations play a critical role in the pathogenesis of glioblastoma (GBM), influencing tumor initiation, growth, and therapeutic response. Among the key driver mutations identified in GBM, the prominent example is the mutation of the epidermal growth factor receptor (EGFR) gene. Dysregulated signaling pathways, including the PI3K/Akt/mTOR, the Ras/Raf/MEK/ERK, and the NOTCH pathway play a critical role in cell proliferation, survival, and invasion in GBM. Epigenetic modifications contribute to tumor initiation, repression of the tumor suppressor genes, and therapy resistance. Global DNA hypomethylation, site-specific hypermethylation, histone deacetylase, microRNAs (miRNAs), and long non-coding RNAs (lncRNAs) are the most common epigenetic modifications. Immune checkpoints, such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are upregulated, leading to T-cell exhaustion and impaired antitumor immune responses. The molecular classification systems have provided a more refined understanding of GBM biology, have important implications for personalized treatment strategies, play a role in guiding clinical trials designed to specifically target and evaluate novel therapies in patients with specific molecular subtypes, and hold promise for predicting treatment response. The identification of molecular subtypes can be associated with different treatment decisions.

Keywords: *glioblastoma, molecular advances, personalized treatment strategies*

Reviews

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1. Introduction

Glioblastoma (GBM) is the most aggressive primary brain tumor with limited treatment options and poor prognosis (1). Despite advancements in surgical techniques, radiation therapy, and systemic therapy, such as the addition of tumor-treating fields to maintenance temozolomide chemotherapy vs maintenance temozolomide alone, remains dismal in terms of median survival of GBM patients (2). In recent years, molecular research has provided valuable insights into the underlying mechanisms of GBM, uncovering key molecular alterations and signaling pathways that drive tumor development and progression. Understanding these molecular advances holds great promise for developing targeted therapies and improved clinical outcomes for GBM patients.

One of the major advancements in GBM research has been the identification of driver mutations that contribute to tumor initiation and progression (3). The dysregulation of the epidermal growth factor receptor (EGFR) signaling pathway has also emerged as a significant molecular alteration in GBM. EGFR alterations, including gene amplification and mutations, are frequently observed and play a critical role in promoting tumor growth, invasion, and therapy resistance (4).

Epigenetic modifications, including deoxyribonucleic acid (DNA) methylation and histone modifications, have been recognized as important contributors to GBM pathogenesis (5). Additionally, non-coding ribonucleic acids (RNAs), such as microRNAs and long non-coding RNAs, have been implicated in GBM biology, functioning as regulators of gene expression and potential therapeutic targets (6).

The interaction between GBM and the immune system has led to the exploration of different strategies for immunotherapeutic treatments that can lead to a better prognosis for patients with glioblastoma (7).

The purpose of this literature review is to summarize and emphasize the significance of molecular advances in glioblastoma research.

2. Discussion

2.1. Driver Mutations

Driver mutations play a critical role in the pathogenesis of glioblastoma (GBM), influencing tumor initiation, growth, and therapeutic response. The mutation of the epidermal growth factor receptor (EGFR) gene is a key driver mutation identified in GBM with significant functional significance, impacting the prognosis, and with potential therapeutic implications.

Mutations in the epidermal growth factor receptor (EGFR) gene are the most frequently observed genetic alterations in GBM, occurring in approximately 50% of cases (8). EGFR alterations include gene amplification, point mutations (e.g., EGFRvIII), and other structural alterations, leading to constitutive activation of the EGFR signaling pathway (9). EGFR alterations contribute to tumor growth, invasion, and therapy resistance through various mechanisms, including enhanced cell proliferation, survival signaling, angiogenesis, and immunosuppression (3). EGFRvIII, a common EGFR variant, is particularly prevalent in GBM and has been associated with a more aggressive phenotype (10). EGFR alterations have prognostic implications, with EGFR amplification and EGFRvIII associated with worse overall survival (11). Targeting EGFR alterations has been a major focus of therapeutic development in GBM. Multiple approaches, including small molecule inhibitors, monoclonal antibodies, and immunotherapies, have been explored in clinical trials, but no EGFR-targeted strategy has been proven efficient in GBM (12).

2.2. Dysregulated Signaling Pathways

The phosphoinositide 3-kinase/protein-kinase B/mammalian (or mechanistic) target of the rapamycin (PI3K/Akt/mTOR) pathway is frequently dysregulated in GBM, promoting cell survival, proliferation, and angiogenesis (13). Activation of this pathway occurs through various mechanisms, including genetic alterations, such as mutations in the PI3K catalytic subunit (PIK3CA) or the loss of phosphatase and tensin homolog (PTEN) tumor suppressor function (14). Therapeutic

targeting of the PI3K/Akt/mTOR pathway has shown promise in preclinical models and early-phase clinical trials. Inhibitors of PI3K, Akt, and mTOR have been developed and tested, either as single agents or in combination with other therapies. However, challenges such as intrinsic and acquired resistance mechanisms, complex feedback loops, and the presence of multiple isoforms within the pathway have limited the success of targeting this pathway in GBM (15). Combination strategies and personalized approaches based on individual pathway alterations may hold promise for improving therapeutic outcomes.

The rat sarcoma virus/ rapidly accelerated fibrosarcoma/ mitogen-activated protein kinase/ extracellular signal-regulated kinase (Ras/Raf/MEK/ERK) pathway is another dysregulated signaling cascade implicated in GBM. Aberrant activation of this pathway occurs through genetic alterations, including amplification or mutations in the epidermal growth factor receptor (EGFR) gene or downstream components of the pathway (16). The Ras/Raf/MEK/ERK pathway regulates cell proliferation, survival, and invasion in GBM. Efforts to target this pathway in GBM have faced challenges due to the complexity of pathway crosstalk, adaptive resistance mechanisms, and the lack of potent and selective inhibitors (17). Clinical trials exploring combination therapies targeting multiple nodes within the pathway or combining pathway inhibitors with other treatment modalities are ongoing, aiming to enhance therapeutic efficacy.

The neurogenic locus (NOTCH) signaling pathway plays a critical role in GBM stem cell maintenance, tumor angiogenesis, and immune modulation (18). Dysregulation of NOTCH pathway components, including NOTCH receptors and ligands, is observed in GBM. Aberrant activation of NOTCH signaling contributes to tumor growth and therapy resistance (19). Therapeutic targeting of the NOTCH pathway in GBM has been challenging, with limited success in clinical trials. Complex cross-talk with other signaling pathways, the presence of multiple NOTCH receptors, and the context-dependent effects of NOTCH signaling pose hurdles in developing effective targeted therapies (20). However, the development of novel approaches, such as gamma-secretase inhibitors and antibody-based therapies, holds promise for future therapeutic interventions.

2.3. Epigenetic Modifications

DNA methylation is a key epigenetic modification that regulates gene expression. In GBM, global DNA hypomethylation and site-specific hypermethylation are commonly observed. Promoter hypermethylation leads to the silencing of tumor suppressor genes, contributing to tumor initiation and progression (21). For example, the methylation of the O^6-methylguanine-DNA methyltransferase (MGMT) gene promoter is associated with increased sensitivity to alkylating agents, such as temozolomide (22). Other genes involved in cell cycle control, DNA repair, and apoptosis are also frequently hypermethylated in GBM (5). DNA methylation profiles have been utilized for molecular classification and prognostication of GBM patients, providing valuable insights into tumor biology (23).

Non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are emerging as key regulators of gene expression and GBM pathogenesis. miRNAs function as post-transcriptional regulators, modulating the expression of target genes. Dysregulation of specific miRNAs in GBM has been linked to tumor growth, invasion, angiogenesis, and therapy resistance (24). These miRNAs can act as oncogenes (oncomiRs) or tumor suppressors, depending on their target genes and downstream signaling pathways. Strategies to restore or inhibit specific miRNAs hold therapeutic potential in GBM treatment (25). Micro-RNAs (miRNAs) are differentially modulated in M059J and M059K cells exposed to ionizing radiation and so miRNA modulation contributes to the resistance to ionizing radiation. (26) Similarly, dysregulation of lncRNAs has been implicated in GBM biology, influencing tumor growth, invasion, and therapy response (27). The role of lncRNA HOXA transcript antisense RNA myeloid-specific 1 (HOTAIRM1) as a driver of biological aggressiveness, radioresistance, and poor outcome in glioblastoma has been demonstrated in recent studies. (28) Targeting

specific lncRNAs may provide novel therapeutic opportunities for GBM patients.

The dysregulation of epigenetic modifications in GBM presents opportunities for the development of targeted therapies. Epigenetic modifiers, such as DNA methyltransferase inhibitors (DNMTi) and HDAC inhibitors, have been investigated in preclinical and clinical settings for GBM treatment. DNMTi, including 5-azacytidine and decitabine, can reverse aberrant DNA methylation patterns, reactivating silenced tumor suppressor genes (29). HDAC inhibitors, such as vorinostat and panobinostat, induce histone acetylation and promote gene expression changes (30). Altered expression/activity of key epigenetic regulators, especially histone deacetylases (HDACs) in GBM stem cells has been associated with poor prognosis; inhibiting the activity of HDACs using histone deacetylase inhibitors (HDACi) has been promising as mono-therapeutic in targeting GBM and in sensitizing GBM stem cells to an existing anticancer regimen (31). Combining epigenetic modifiers with other treatment modalities, such as chemotherapy or immunotherapy, holds promise for synergistic effects and improved outcomes (32). Furthermore, targeted therapies specific to dysregulated miRNAs and lncRNAs are being explored as potential interventions (33).

2.4. Immune Dysregulation

Immune checkpoint dysregulation is a key mechanism employed by GBM to evade immune surveillance. Immune checkpoints, such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), regulate immune responses and maintain immune homeostasis. In GBM, these checkpoints are upregulated, leading to T-cell exhaustion and impaired antitumor immune responses (34). Targeting immune checkpoints (TAMs) using checkpoint inhibitors has shown promising results in various malignancies, leading to the restoration of T-cell function and enhanced antitumor immune responses (35). Checkpoint inhibitors, such as anti-PD-1 and anti-CTLA-4 antibodies, aim to unleash the antitumor immune response by blocking immune checkpoint pathways and reinvigorating T-cell activity (36). CAR T-cell therapy involves genetically engineering patients' own T cells to express receptors specific to tumor antigens, enhancing their tumor recognition and killing abilities (37).

TAMs, which include macrophages and microglia, are major components of the immune infiltrate in GBM. TAMs have distinct polarization states, with the M2-like phenotype being predominant in GBM. M2-like TAMs exhibit immunosuppressive functions and promote tumor growth, angiogenesis, and invasion (38). The interaction between TAMs and GBM cells creates an immunosuppressive microenvironment that inhibits effective antitumor immune responses. Targeting TAMs and reprogramming them towards an M1-like phenotype, which exhibits antitumor activity, represents a potential therapeutic strategy (39).

The tumor microenvironment in GBM is characterized by immunosuppressive factors and signaling pathways that promote immune evasion. Immunosuppressive factors, such as transforming growth factor-β (TGF-β), interleukin-10 (IL-10), and indoleamine 2,3-dioxygenase (IDO), inhibit immune cell function and promote tumor tolerance (40). Additionally, GBM cells release factors that attract immunosuppressive cells, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), further contributing to immune suppression (41).

Despite the promise of immunotherapy, several challenges exist in applying these approaches to GBM. The limited infiltration of immune cells into the tumor poses hurdles to effective immunotherapy delivery and efficacy (42). Overcoming these challenges requires the development of innovative strategies, such as local delivery methods, combination therapies, and the use of immune modulators to overcome immune suppression and enhance the therapeutic response (43).

2.5. Precision Medicine and Molecular Classification

The 2021 WHO classification adds several newly recognized tumor types and makes several important changes to principles relating to nomenclature, grading, and classification of CNS tumors, many of these

changes increase the reliance on molecular alterations for disease classification and elevate the importance of molecular testing in diagnosis, treatment and prognosis (gliomas including glioblastoma, IDH-mutant astrocytic gliomas encompassing astrocytomas and oligodendroglioma, ependymomas and meningiomas). In the current classification, all IDH-mutant diffuse astrocytic tumors are considered a single type (Astrocytoma, IDH-mutant) and are then graded as CNS WHO grade 2, 3, or 4. Glioblastoma, IDH-wildtype should be diagnosed in the setting of an IDH-wildtype diffuse and astrocytic glioma in adults if there is microvascular proliferation or necrosis or TERT promoter mutation or EGFR gene amplification or +7/−10 chromosome copy number changes (44,45).

One of the most influential molecular classification efforts in GBM is The Cancer Genome Atlas (TCGA) project. The TCGA classification stratifies GBM into several distinct molecular subtypes based on comprehensive genomic and transcriptomic analyses (3). These subtypes include classical, mesenchymal, proneural, and neural subtypes, each characterized by specific molecular features and signaling pathway dysregulations. For instance, the classical subtype is associated with alterations in the epidermal growth factor receptor (EGFR) pathway, while the mesenchymal subtype shows enrichment for immune response-related genes and mesenchymal markers (23).

The molecular classification systems, such as the TCGA classification, have provided a more refined understanding of GBM biology and have important implications for personalized treatment strategies. By identifying specific molecular alterations within subgroups of GBM, these classification systems enable the development of targeted therapies aimed at disrupting the dysregulated signaling pathways unique to each subtype. For instance, EGFR inhibitors, such as erlotinib and gefitinib, have shown potential efficacy specifically in GBM patients with EGFR amplification or mutations (3).

Molecular classification also plays a crucial role in guiding the design of clinical trials for GBM. By considering the molecular characteristics of the tumor, clinical trials can be designed to specifically target and evaluate novel therapies in patients with specific molecular subtypes. This approach allows for more precise patient selection and potentially improves the chances of therapeutic success. For example, clinical trials may focus on evaluating immune checkpoint inhibitors in patients with the mesenchymal subtype, which is associated with immune response-related gene expression and may be more responsive to immunotherapy (46). By tailoring clinical trials based on molecular subtypes, researchers can better assess treatment efficacy and response rates within specific patient populations.

In addition to guiding treatment strategies and clinical trial design, molecular classification systems in GBM also hold promise in predicting treatment response. The identification of molecular subtypes associated with distinct clinical outcomes can aid in patient risk stratification and inform treatment decisions. For instance, the proneural subtype, characterized by IDH mutations, is associated with a better prognosis and may require less aggressive treatment compared to other subtypes (5).

2.6. Future perspectives

Future perspectives in molecular advances for glioblastoma present exciting opportunities for improved diagnosis, treatment, and patient outcomes. The identification of novel molecular targets holds the potential to develop more effective therapies tailored to individual patients. With advancements in genomic profiling, precision medicine approaches will become more commonplace, allowing for personalized treatment strategies based on the molecular characteristics of each patient's tumor. Additionally, the integration of artificial intelligence and machine learning algorithms will enhance the analysis of large-scale molecular data, leading to improved prognostic models and treatment predictions. Furthermore, ongoing research on immunotherapies, including immune checkpoint inhibitors and CAR-T cell therapy, offers promising avenues for targeting the immune system to fight glioblastoma, for example, adding an autologous tumor lysate-pulsed dendritic cell vaccine to standard therapy is feasible and safe in glioblastoma patients, and may extend survival (47).

Combination therapies that target multiple molecular pathways simultaneously are also being explored, aiming to overcome tumor heterogeneity and resistance mechanisms. Collaborative efforts among researchers, clinicians, and industry partners will be vital in translating these molecular advances into clinical practice, ultimately improving the prognosis and quality of life for glioblastoma patients in the future.

3. Conclusions

The recent molecular advances in GBM research have provided deeper insights into the underlying mechanisms driving tumor development and progression. The identification of driver mutations including the epidermal growth factor receptor (EGFR) gene, dysregulated PI3K/Akt/mTOR, Ras/Raf/MEK/ERK, the NOTCH signaling pathways, epigenetic modification as DNA hypomethylation, and non-coding RNAs, and immune dysregulation, such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) has opened up new avenues for targeted therapies and immunotherapeutic approaches. These molecular advancements hold great potential for personalized treatment strategies, designed clinical trials to specifically target and evaluate novel therapies in patients with specific molecular subtypes, and also improving the prognosis and outcomes for GBM patients, offering hope for a brighter future in the management of this devastating disease.

Abbreviations:

GBM – Glioblastoma
EGFR – Epidermal growth factor receptor
PI3K/Akt/mTOR – Phosphoinositide 3-kinase/protein-kinase B/mammalian (or mechanistic) target of the rapamycin
Ras/Raf/MEK/ERK – Rat sarcoma virus/ rapidly accelerated fibrosarcoma/ mitogen-activated protein kinase/ extracellular signal-regulated kinase
α-KG – Isocitrate to α-ketoglutarate
TCA – Tricarboxylic acid cycle
2-HG – 2-hydroxyglutarate
PI3KCA – PI3K catalytic subunit
PTEN – Phosphatase and tensin homolog tumor suppressor
MGMT – O^6-methylguanine-DNA methyltransferase
HDACs – Histone deacetylases
PRC2 – Polycomb repressive complex 2
miRNAs – microRNAs
lncRNAs – Long non-coding RNAs
HOTAIRM1 – lncRNA HOXA transcript antisense RNA myeloid-specific 1
DNMTi – DNA methyltransferase inhibitors
PD-1 – Programmed cell death protein 1
CTLA-4 – Cytotoxic T-lymphocyte-associated protein 4
TGF-β – Transforming growth factor-β (TGF-β)
IL-10 – Interleukin-10
IDO – Indoleamine 2,3-dioxygenase (IDO),
Tregs – Regulatory T cells
MDSCs – Myeloid-derived suppressor cells
CAR – Chimeric antigen receptor
TCGA – The Cancer Genome Atlas

Statements:

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The Outcomes of Intensity Modulated Radiotherapy versus Conventional 2D Radiotherapy in Patients with Oropharyngeal or Hypopharyngeal Squamous Cell Carcinoma. A Case-Control Study

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Abstract

Introduction: Head and neck cancers' radiotherapy (RT) is challenging due to the irregular target volumes and the proximity of multiple organs at risk. The purpose of this study is to compare the toxicity, loco-regional control and the pattern of tumour recurrence after intensity modulated radiotherapy (IMRT) or conventional 2D radiotherapy (2D CRT) in patients with squamous cell carcinoma (SCC) oropharyngeal or hypopharyngeal cancers.

Material and method: We retrospectively compared the outcomes of SCC oropharyngeal or hypopharyngeal cases treated by IMRT or 2D CRT from 1998 to 2010 in a Canadian Academic Hospital. We matched the patients in the two groups according to primary tumour location and clinical stage. The information on treatment, toxicity and outcomes was retrieved from patients' medical records. For the patients having a recurrence after IMRT, the CT scan at relapse was fused with the planning CT. For the patients recurring after 2D CRT, we matched the CT images with the relative position of the radiotherapy fields. Statistical analysis was made using GraphPad Prism software.

Results: We included a total of 50 patients in the IMRT group and 50 in the 2D CRT group. The median age was 62 and 58 years, respectively, and the median follow-up was 18 and 22.6 months, respectively. Some of the side effects were less frequent on the IMRT group compared to the 2D CRT: xerostomia (16% vs 64%, P=0.0036), mucositis (70% vs 74% P=0.5451), weight loss (18% vs 46% P= 0.0027), radionecrosis/mandibular fracture (0 % vs 2%), fibrosis (0% vs 10%), and telangiectasia (0% vs 4%). However, acute dermatitis and late dysphagia were more frequent in the IMRT group (44% vs 28% P=0.0042; and 14% vs 2% P=0.028; respectively). The overall survival at 2 years was for 74.03% for IMRT and 60% for 2D CRT (P< 0.001) and the 5 years actuarial locoregional control was 89.54 % for IMRT group, and 62.48% for the 2DCRT

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group (P< 0.001). Three patients from the IMRT group had a local recurrence (2 in-field and 1 marginal), while in the 2D-CRT group, there were 10 patients with a local recurrence (6 in-field and 4 marginal).

Conclusion: SCC oropharyngeal and hypopharyngeal patients treated with IMRT and concurrent cisplatin had better outcomes and fewer side effects, when compared to similar cases treated with 2D CRT. The local recurrence had a similar pattern for both techniques.

Keywords: *IMRT, 2D CRT, radiotherapy, oropharyngeal cancer, outcome, recurrence*

1. Background

Intensity Modulated Radiotherapy (IMRT) was first introduced 30 years ago and is already established as the preferred technique for treating head and neck cancers (HNC).

The transition from 2D CRT to 3D CRT and then to more conformal techniques like IMRT/VMAT was made at a different pace in various regions and institutions. Higher spatial accuracy allows a better sparing of the organs at risk (OARs) allowing the decrease of the side effects. However, new technology implementation needs to be made while understanding the necessary challenges in planning, delivery, and quality assurance.

For oropharyngeal cancer patients the IMRT reduced the toxicity without worsening the clinical outcomes when compared with 2D/3DCRT, according to a review of the literature and meta-analysis by *Alterio et al* (1). For hypopharyngeal cancers, a retrospective analysis of technological improvements' clinical impact concluded that overall survival (OS), progression free survival (PFS) and freedom from local recurrence were improved with IMRT over 2D-RT and reduction in acute toxicity was observed (2).

However, there is also conflicting data in the literature. A systematic review and meta-analysis of the outcomes of IMRT vs 2D/3D CRT in HNC patients treated with curative intent was performed by Gupta et al and included 1155 patients from 7 randomized controlled trials. For the nasopharyngeal cancer patients the use of IMRT was translated into a relative reduction in the risk of loco-regional relapse and in the risk of death of 24% and 30%, respectively, compared to 2D/3D CRT. However, this benefit was not found for pharyngeal and laryngeal cancers. The evidence for IMRT use resulting in reducing moderate to severe acute and late xerostomia compared to 2D/3D-RT was considered as consistent but moderate-quality (3).

In the early days of IMRT implementation unusual side effects were seen, caused by a high dose delivered in non-target areas. It was the result of plan optimisation process in the context of delineating only the proximity OAR or a limited number of OAR (4). Additional data regarding the side effects of IMRT RT compared to 2D/3D CRT and the local recurrence patterns may lead to identifying new sensitive structures, avoid common errors and improve the clinical practice.

The primary objective of this study was to compare the early and late side effects (grade 2 or more) for IMRT and 2D CRT, respectively, in patients with oropharyngeal or hypopharyngeal cancer. Loco-regional control and patterns of recurrence analysis were secondary objectives.

2. Methods

2.1. Study design

Using a matched case-control design, we compared a cohort of patients diagnosed with oropharyngeal or hypopharyngeal squamous cell carcinoma (SCC) treated with IMRT (2004-2010) with a similar historical cohort treated in the same institution with 2D CRT(1998-2004). Matching has been done by the tumour site and stage. A review of the medical records up to 2022 has been done to assess the toxicity profile, locoregional control and the pattern of tumour recurrence.

2.2. Patients' selection

The study included patients with oropharyngeal or hypopharyngeal SCC who were treated with curative intent. We excluded the patients with carcinoma of the base of the

tongue (due to wide individual variability in target volume delineation and inaccurate assessment of the extent of recurrence on CT scan) and those with other synchronous primary tumour and/or those receiving biological therapy.

2.3. Staging, response evaluation and toxicity grading

The staging was done according to the AJCC staging manual 2010 (The 6th edition). Evaluation of the response to treatment was done using the WHO criteria. Toxicity grading was performed according to the NCIC common toxicity criteria version 4.03. Weight loss was defined as a non-voluntary decrease of at least 3 kg during radiotherapy.

For patients treated with IMRT the review of the radiotherapy plans was done by reviewing the charts on the planning system, while for patients treated with 2D CRT it was done by reviewing the patients' radiotherapy charts together with the x-ray check films. The tumour recurrence analysis was made together with a Radiologist for the conventional radiotherapy group, using CT scans/MRI.

2.4. Workflow (IMRT)

The simulation was done using a thermoplastic mask and multislice CT simulator with slice thickness from 2 to 5 mm, iv contrast and fusion with diagnostic MR.

Delineation of the target volumes and the organs at risk (OAR) was done according to the ICRU 50, 62 or 83 reports' definitions (The ICRU 83 for IMRT). In definitive radiotherapy, delineation of the gross tumour volume (GTV) was done based on imaging and clinical examination. In most cases a margin of 0.3 cm was added around the spinal cord and the brainstem to obtain planning risk volume (PRV)

The high-risk clinical target volume (CTV) included the GTV primary and nodal plus a margin of 0.7 – 1cm. In N0 lymph nodes, CTV low risk was delineated according to the DAHANCA, EORTC, GORTEC, and RTOG consensus guidelines. The planning target volume (PTV) was delineated by adding a margin of 0.3 - 0.5 cm to the corresponding CTV. The radiotherapy doses were prescribed to the PTVs. Five cases were done by forward planning (treated by step and shoot technique) but the majority of cases were done by inverse planning and treated by sliding window technique. Doses to OARs were kept within the tolerance limits according to the local protocols, based on international recommendations.

IMRT treatment delivery was done using 6MV linear accelerators by (3 – 9) angled beams using the Simultaneous Integrated Boost (SIB) technique in most cases. Concurrent weekly Cisplatin 40 mg/m2 was used in most of the patients.

At recurrence, fusion of the new CT/MRI or PET scan with the planning CT scan has been performed. The recurrence was considered as “in field” if 25-95% of its volume was located in the high dose region, “marginal” for a value of 5-25% and “out-of-field” for less than 5%.

2.5. Workflow (2D CRT)

Conventional radiotherapy had been planned using the conventional simulator and two lateral opposing fields matched with the low anterior neck field.

Treatment delivery had been performed using the cobalt unit and 6 MV linear accelerators. Patients had been treated up to 45 Gy to the lateral opposing fields to the neck then off-cord. Patients with residual lymph nodes in the posterior neck had been boosted by a 9 MeV electron beam.

Localization of the site recurrence either in the high dose region (60 Gy or more) or low dose region (< 60 Gy) or both has been done using the CT data describing the site of recurrence and its maximal 3D diameters then multiplying them to obtain the volume of recurrence and correlating that volume to the conventional 2D radiotherapy fields (on the x-ray check films) in relation to a bony landmark (e.g the hyoid bone). For example, if the majority of recurrent tumour is located above the hyoid bone it is considered in the high dose region and if it is located in the low anterior neck region it is considered in the low dose region.

3. Results

This study included 50 patients treated using 2D CRT (1998-2004) and 50 patients treated using IMRT (2004-2010). Patient details and treatment characteristics are presented in Table 1 and Table 2.

Table 1. Patients' characteristics in the two groups

	IMRT(N=50)		2D CRT (N=50)	
	value	*%*	**value**	*%*
Age (Median)	62 years		58 years	
Smoking	18	*36%*	16	*32%*
Alcohol	21	*42%*	19	*38%*
Sex				
Male	18	*36%*	27	*54%*
Female	32	*64%*	23	*46%*
Primary tumour location				
Tonsil	31	*62%*	30	*60%*
Pharingeal wall	9	*18%*	8	*16%*
Soft palate	5	*10%*	0	*0%*
Pyriform synus	4	*8%*	11	*22%*
Postrcricoid	1	*2%*	1	*2%*
T stage				
T1	12	*24%*	8	*16%*
T2	15	*30%*	13	*26%*
T3	14	*28%*	7	*14%*
T4	19	*38%*	22	*44%*
N stage				
N0	0	*0%*	4	*8%*
N1	7	*14%*	11	*22%*
N2a	6	*12%*	9	*18%*
N2b	6	*12%*	4	*8%*
N2c	5	*10%*	2	*4%*
N3a	7	*14%*	4	*8%*
N3b	19	*38%*	16	*32%*

** IMRT – Intensity Modulated Radiotherapy; 2D CRT – 2D Conformal Radiotherapy; N – Number; RT – Radiotherapy*

Table 2. Treatment details for the SCC oropharynx and hypopharynx patients in the two groups

	IMRT(N=50)		2D CRT (N=50)	
	value	*%*	**value**	*%*
RT dose (Gy)				
Median	67.5		66	
Range	60-70			
Number of fractions				
Median	30		33	
Range	30-33			
Treatment type				
Definitive RT	45	*90*	38	*76*
Adjuvant RT	5	*10*	12	*24*
Concurrent Cisplatin	38	*76*	5	*10*
PEG	40	*80*	0	*0*

** IMRT – Intensity Modulated Radiotherapy; 2D CRT – 2D Conformal Radiotherapy; N – Number; PEG – percutaneous endoscopic gastrostomy.*

3.1. Side effects

In the IMRT group there were significantly less patients developing acute (moderate) grade 2 or more ***xerostomia*** (16% vs 64%, P=0.0036) as identified during weekly clinical exams and reported according the NCIC common toxicity criteria. There was also less frequent ***weight loss*** (18% vs 46%, P=0.0027) compared to the 2DCRT group. The 8 patients who experienced xerostomia in IMRT cases were stage IVa and IVb (Table 3). Dmean for the ipsilateral parotid glands was 23.28 Gy to a volume of 21.26 cc and Dmean for the contralateral parotid gland was 19.79 Gy to a volume of 20.09 cc, respectively. The odds ratio for observed xerostomia grade 2 or more was 0.10.

In the IMRT group there were more patients reporting acute ***dermatititis*** (44% vs 28%, P=0.0042, OR 2.02) and ***dysphagia*** (grade 2 or more) (14% vs 2%, P=0.0284).

Acute ***mucositis (grade 2 or more***) was almost equally reported for IMRT and 2D CRT (70% vs 74%, P=0.5451, OR 0.61). Other acute side effects like laryngitis and otitits media were rare and the difference between the two techniques was not relevant (Figure 1).

Table 3. Anatomical site and clinical stage of patients treated with IMRT and developing acute xerostomia

Primary tumor anatomic site	T	N	Stage
Soft palate	2	2c	IVa
Tonsil	2	2b	IVb
Tonsil	2	2b	IVa
Tonsil	4	2a	IVb
Tonsil	1	2b	IVa
Tonsil	4	2b	IVb
Pyriform sinus	4	1	IVa
Pyriform sinus	4	0	IVa

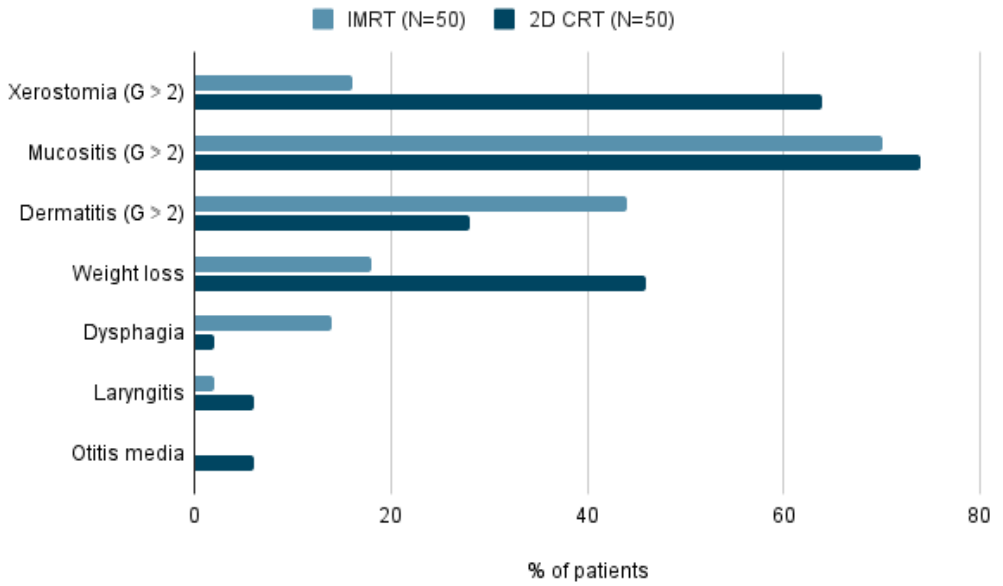

Figure 1. Radiotherapy acute side effects in oropharyngeal and hypopharingeal SCC in two matching case-control groups treated with 2D CRT or IMRT

Late ***skin*** side effects were significantly less frequent in patients treated with IMRT compared with 2D CRT; Radiation-induced ***osteonecrosis*** and ***fracture of the mandible*** were not reported for IMRT but were reported in one patient (2%) in 2D CRT (P = 0.4361).

Two patients of those who had acute dysphagia in the IMRT group subsequently developed ***esophageal stenosis*** and underwent endoscopic dilatations. ***Hypothyroidism*** was reported in 16% of patients receiving 2D CRT but thyroid function tests were not routinely requested for patients receiving IMRT. Late xerostomia was reported in 8 patients (16%) in the IMRT group versus 32 patients (64%) in the 2D CRT group.

3.2. Outcomes

The response rate assessed at 2 months after treatments' end was 93% for IMRT and 89% for 2D CRT. The median follow-up in the IMRT group was 18 months and in the 2D CRT was 22.6 months. The overall survival at 2 years was 74% for IMRT and 60% for 2D CRT (P< 0.001). The 5-year actuarial locoregional control (LRC) was 89.5% for IMRT and 62.48% for 2D CRT (P<0.001). The multivariate analysis identified IMRT as an independent factor for improving the locoregional control (P = 0.0102).

Local recurrence was seen in 3 patients (6%) in the IMRT group versus 10 patients (20%) in the 2D-CRT group (P= 0.0377, OR 0.25). In the IMRT group 2 of them recurred in the high dose PTV (in-field) and the 3rd patient's recurrence was marginal (Table 4). Two out of the 3 patients who recurred were treated by the step-and-shoot technique. In the 2D CRT group 6 patients had in-field recurrences and 4 patients had borderline recurrences**.** Patients experiencing local recurrences did not have any treatment gaps.

Distant metastases were almost equal in the two groups (6 patients treated with IMRT and in 7 patients treated with 2D CRT).

Table 4. Clinical details of the local recurrence of cases in the IMRT group

Primary tumour site	Stage	RT dose	Recurrence site	Recurrence category	Concurrent Cisplatin
soft palate	T3N2M0	70Gy/35 fr 50 Gy/25 fr	level II	in-field	yes
oropharyngeal wall	T4N2M0	70Gy/33 fr 50.4Gy/28 fr	posterior oro-pharingeal wall	in-field	yes
tonsil	T2N1M0	60Gy/25 fr 50 Gy/25 fr	tonsil peri-epiglotic space level II	marginal	no

4. Discussion

We performed a comparative analysis of the treatment outcomes for two matched case-control groups of patients diagnosed with SCC of oropharynx or hypopharynx treated either with IMRT or 2D CRT in an academic Canadian hospital.

As expected, some of the acute side effects, like ***xerostomia***, were significantly less frequent in the IMRT group compared to 2D CRT (16% vs 64%, P=0.0036). The patients

receiving IMRT and developing xerostomia had extensive primary tumour and nodal involvement, which hampered the parotid gland sparing. A mean dose equal or higher to 26 Gy to the parotid gland is correlated to a significant decrease for the stimulated salivary flow (5). The PARSPORT trial compared IMRT to 3D CRT and reported significantly lower rates of xerostomia in the IMRT group than in the conventional radiotherapy group (38% vs 74% at 12 months, P=0.0027) (6). However, except for the difference in the treatment technique, and the time of assessing it, xerostomia evaluation was more accurate in this study, salivary flow measurements being conducted. A recently published cohort study compared radiation-induced xerostomia and quality of life for HNC patients treated with either IMRT or 3D CRT. The measured salivary flow, excretion fraction on scintigraphy and xerostomia-related quality of life were all superior in the IMRT arm (7).

Mucositis had almost the same frequency in both groups (70% vs 74%, P = 0.5451, OR 0.61), despite the higher use of concurrent Cisplatin in the IMRT group. In a study published in 2005 included 450 HNC patients treated by 154 USA radiation oncologists, the rate of moderate and severe acute oral mucositis was 35% and 28%, respectively. A cumulative dose above 50 Gy, concomitant chemotherapy and nasopharyngeal/oropharyngeal location were risk factors for severe oral mucositis. The majority of patients were treated with conventional fractionation but the details on technique were not mentioned (8).

Acute Grade 2 or 3 ***dermatitis*** was significantly more frequent for the IMRT group compared to 2D CRT group (44% vs 28%, P=0.0042, OR 2.02). The explanation might be the lower skin-sparing effect due to the oblique incidence of the photon beams used for IMRT. A scoring system incorporating clinical and dosimetric factors (age, body mass index and concurrent chemotherapy status and V60 Gy delivered on 5 mm within the body contour) proved to be useful in predicting dermatitis occurrence for HNC patients treated with IMRT (9).

Weight loss of at least 3 kg was reported in 18% of patients treated with IMRT vs 46% for 2D CRT (P=0.0012). This may be due to the fact that most patients in the IMRT group had a percutaneous endoscopic gastrostomy (PEG) feeding tube placed, allowing them to have an adequate caloric intake during treatment. Predictive factors for weight loss during HNC RT were analyzed in many studies. In a group of 87 patients treated with 3D CRT 48.7% had severe weight loss (>5% of the body mass), which was more frequent at higher doses and in younger patients. Advanced tumour stage and combined treatment modality (surgery, RT and chemotherapy) were risk factors for weight loss, but body mass index without the assessment of body composition was not a reliable factor (10). Data from a prospective cohort of HNC patients treated with either 3D CRT or IMRT showed that the risk of losing more of 10% of body weight was higher for radical RT compared to adjuvant RT and for 3D CRT compared with IMRT. The maximum weight loss was on the third and fourth week of treatment and 40% of patients had a weight gain during the first week (11).

IMRT has a steep dose gradient which allows dose escalation to target volumes, dose reduction to the organs at risk and therapeutic ratio improvement. A dose of 67.5 Gy/30 fractions in IMRT group is biologically as effective as 70 Gy/35, significantly higher than 66 Gy/33 fractions used in the 2D CRT. Dose per fraction was higher for some volumes in the IMRT group, which increase the risk of late side effects.

Except for dysphagia, caused by oesophageal stricture in two patients, we did not observe an increase of the ***late toxicity*** in the IMRT group. In our study xerostomia was reported in 16% in the IMRT group vs 64% of patients in the 2 DCRT group. The difference in percentages of xerostomia is probably due to the fact that IMRT allowed rapid fall of the dose beyond the target volume/s and hence

it led to parotid sparing. On the other hand, the use 2D radiotherapy included larger volumes of the normal tissues including the parotid gland which led to more early and the late side effects especially xerostomia. Our results are in line with those reported by a systematic review on treatment outcomes and toxicity after RT for HNC, which identified late xerostomia as significantly more frequent in patients treated with 2D or 3D CRT (12).

An interesting evaluation of dose-volume and dose-length parameters in HNC patients treated with 3D CRT or IMRT showed that V54, V60, and lengths receiving circumferential disease higher than 50 Gy and 54 Gy at cervical oesophageal level were significantly higher for patients receiving IMRT compared to 3D CRT. At minimum 4 years post treatment 30% of patients in the IMRT group and 15% of patients in the 3D CRT group had documented symptomatic oesophageal strictures (13). These findings underline the importance of delineating and sparing anatomical structures formed by late-responding normal tissues and follow-up patients on long term.

In our study, the 5-year actuarial ***LRC*** was significantly longer in the IMRT group compared to the 2D CRT group (89.54% vs 62.48%, P<0.0001) but the difference might be due to other factors except for the radiotherapy technique. Concurrent cisplatin was received by most of the patients treated with IMRT and most probably contributed to the better outcomes. However, the IMRT technique was an independent factor for improving the locoregional control. Similarly, the systematic review by *Koulolias et al* reported 83.6% LRC for IMRT and 74.4% for 2D and 3D CRT at 3 years (P = 0.025) (12).

We analyzed the spatial location of the local recurrence in relation with the treatment fields and observed that in the 2D CRT group, 6 patients had in-field local recurrence and 4 had a marginal recurrence. Since the weight loss was reported in almost half of the 2D CRT patients, there is a higher risk of intrafractional motion within the immobilization mask or geometrical target displacement, leading to a suboptimal coverage.

In the IMRT group 3 patients had a local recurrence. The two patients having in-field recurrence had initial extensive stage, and the one having marginal recurrence did not receive concurrent chemotherapy.

IMRT implementation made possible the OARs sparing, which raised concerns about increasing the risk of regional recurrence due to exclusion of some volumes which could harbour subclinical disease. Except for isolated reports, most of the studies did not confirm this hypothesis. Reporting the relapse pattern made possible creating and updating contouring guidelines for the HN cancers. *Dawson et al* reported recurrence patterns after parotid sparing RT in a group of patients treated with 3D CRT or IMRT. There were no failures in the tissue adjacent to the spared parotid gland, but four patients developed in-field recurrences in the jugulodigastric nodes with superior extensions in the ipsilateral neck (14). After that, consensus guidelines have been published suggesting the superior limit of level 2 nodes to be at the caudal edge of the transverse process of C1 (15).

Chao *et al* reported a 2-year actuarial locoregional control rate of 85% and an ultimate locoregional control rate after surgical salvage of 89%. In this study, there was only one marginal recurrence, located in the region adjacent to the spared parotid gland. This was in a patient with a T3N0 piriform fossa tumour treated post-operatively where recurrence was in the level II nodal region adjacent to the spared parotid gland. Of the 11 in-field recurrences, 9 were within the high-dose CTV and 2 within the low-dose CTV *(16).*

The limitations of our study come from the relatively low number of cases, limited follow-up, and the incomplete information inherent in retrospective studies. Despite our efforts to match patients on primary tumour site and staging, there are some differences between the two groups. There were also some differences in the individual percentages of T or N stage, even the patients were matched

on combined TNM staging the percentage of surgical patients was higher in the 2D CRT group, so the treatment response, for example, could not have been evaluated in those patients. Concurrent chemotherapy was given to the majority of IMRT cases, which would be expected to influence both the treatment toxicity and outcomes. The outcomes were indeed better, but the toxicity was not higher in this group, which shows that the relative reduction of the toxicity by IMRT compared to 2D CRT counterbalanced the additional increase of toxicity caused by the use of the chemotherapy.

However, to the best of our knowledge this is the first case-control study comparing 2D-CRT and IMRT for oropharynx and hypopharynx SCC. Our results illustrate the necessity of delineating the skin and cervical oesophagus as organs at risk for the IMRT treatments in order to decrease the risk of acute and late toxicity. Closing the care gap in the low- and middle-income countries may imply an accelerated transition from 2D to IMRT, situation in which our results might be helpful, as transition experience. Information on the site of relapse and the patients developing xerostomia, especially for the IMRT cases, can help clinicians estimate the risk on similar cases.

5. Conclusion

The use of concomitant radiochemotherapy delivered by IMRT decreased the toxicity, except for acute dermatitis and late dysphagia, improved the locoregional control and overall survival in patients with oropharyngeal and hypopharyngeal SCC, when compared with patients treated with 2D CRT. The recurrence pattern was similar for IMRT and 2D RT.

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Optimization of Lung and Mediastinal Tumor Diagnosis Using Fluoroscopic-Guided Transthoracic Puncture-Biopsy

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Abstract

Introduction: Pathological confirmation of a newly identified tumor is mandatory to create an adequate treatment plan. Patients may have multiple health comorbidities, making them unsuitable for traditional invasive diagnostic procedures. The percutaneous transthoracic biopsy is a minimally invasive alternative method that can provide tissue samples to identify, diagnose, and classify lung or mediastinal tumors.

Materials and methods: Data from patients who underwent fluoroscopic-guided transthoracic needle biopsy (FGTNB) in a tertiary cancer center in the Republic of Moldova from 2019 to 2021 were collected retrospectively.

Results: We identified 54 patients with lung and 12 with mediastinal tumors. In the lung tumor group, the median age was 57 years; in the mediastinal tumor group, the median was 27.5 years. Most lung tumors were situated in the superior lobes (79.6%) and were found to be less than 5 cm in diameter (70.4%). Most mediastinal tumors were anteriorly located (66.7%) and were found to be more than 10 cm in diameter (58.3%). The sensitivity of transthoracic percutaneous biopsy was 79.6% in lung tumors and 83.3% in mediastinal tumors. The patients we biopsied were identified with either malignancy, infectious pathology, or pulmonary fibrosis. Transthoracic needle biopsy of the lung showed a low rate of pneumothorax (5.6%) and a low rate of bleeding (3.7%). Mediastinal tumor biopsy had a rate of pneumothorax of 16.7%, significantly higher than lung biopsy.

Conclusion: Transthoracic needle biopsy performed under fluoroscopic guidance is a safe and efficient alternative diagnostic procedure for comorbid patients with lung or mediastinal tumors.

Keywords: *needle – transthoracic biopsy, lung tumors, mediastinal tumors, diagnosis*

Original Research

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1. Introduction

Lung cancer is the most common cancer in the world and the leading cause of cancer death worldwide. Central lung cancer with airway obstruction is generally sampled bronchoscopically. Computed tomography (CT)-guided or Fluoroscopic-Guided Transthoracic Needle Biopsy is reserved for lesions difficult to visualize sonographically due to bony or paravertebral localization of the intervention. Lung biopsy is a reliable procedure performed to inform treatment strategy for patients with abnormal findings of the lung. Cytology of biopsy specimens has long been a major diagnostic modality for initial evaluation of patients with lung cancer (1,2).

However, invasive diagnostic procedures can be challenging or impossible in patients with multiple underlying health conditions.

The prevailing lung biopsy techniques that are used today encompass the Percutaneous Transthoracic Lung Biopsy, Open Lung Biopsy, Video-Assisted Thoracic Surgery, Transbronchial Biopsy, and Cryo-biopsy (3). Mediastinal cancers, typically diagnosed in younger patients, often have diverse origins and prognostic factors, so a specific pathologic diagnosis is mandatory due to the array of possible differential diagnoses. Surgeons commonly employ thoracoscopy (including video-assisted thoracoscopic surgery) and mediastinoscopy to obtain tissue samples for histopathologic analysis. Various diagnostic possibilities also exist for transbronchial or transesophageal endoscopic techniques, with or without ultrasonic guidance (4).

Fluoroscopic-guided transthoracic needle biopsy (FGTNB) is a minimally invasive technique with a high degree of diagnostic accuracy, which offers the possibility of obtaining sufficient material for cytological and histological research. This method is particularly beneficial for patients with unresectable tumors, concurrent diseases that pose a significant risk for radical surgery, or those who refuse surgery, where the traditional histopathological diagnosis is unachievable (5).

When obtaining a biopsy in mediastinal tumors proves challenging or repeated biopsies yield negative results, there may be a calculated need to resort to parasternal mediastinotomy. When biopsy results for lung tumors remain inconclusive, a comprehensive discussion with the multidisciplinary team may warrant the performance of thoracotomy or median sternotomy. A separate study conducted in the Department of Thoracic and Abdominal Surgery in 2013 reported a false-negative rate for detection of malignancy by percutaneous biopsy of only 5%.

This study is focused on presenting the outcomes of FGTNB in diagnosing both lung and mediastinal tumors.

2. Material and Method

We enrolled patients with lung or mediastinal tumors admitted to the Department of Thoracic and Abdominal Surgery of the Oncological Institute of Chișinău, Republic of Moldova, from 2019-2021. The criteria for inclusion were the ineligibility for general anesthesia and the technical accessibility of the tumor. The superior-anterior part of the mediastinum or segment 3 of the upper lobe were considered as the most accesible locations. The exclusion criteria for the procedure were a performance status of 3 or 4, coagulation disorders, and an estimated life expectancy of less than two months. Tumours with endobronchial extension were primarily refferedd for bronchoscopy. FGTNB was performed in these patients only if the bronchiscopy was unavailable or unfeasible. We conducted a retrospective review of data from the patients' clinical records.

A transthoracic needle biopsy guided by chest radioscopy was performed in these patients. The Bard Biopsy-Gun system was used to biopsy the lesions with Tru-cut needles with a diameter of 16–18G. The needle gauge was selected according to the characteristics of the lesion: tumors larger than 4 cm or with signs of parietal invasion were biopsied with larger gauge needles.

Histopathological identification of the biopsied tissue was obtained in the Cytopathology Department using the Romanowsky-Giemsa coloration method.

3. Results

A total of 66 patients met the inclusion criteria. Severe concomitant pathologies were present in 31 cases (47.0%), advanced local tumors with distant metastases in 23 patients (34.8%), and mediastinal compression syndrome in 12 patients (18.2%). Fifty-four

patients had lung tumors, and 12 patients had mediastinal tumors.

Most patients with lung tumors were older than 50 (85.2%). On the contrary, two-thirds of the patients with mediastinal tumors were under 30 (66.7%). Most lung tumors (70.4%) were less than 5 cm, and more than half of the mediastinal tumors were more than 10 cm in diameter (58.3%). Detailed information on both patient groups can be found in Table 1.

All patients were initially investigated by radiography or radioscopy. Prior to the admission in the Oncology Institute, where CT investigation was not available, a thoracic CT was performed in other clinics for 59.3% (n=32) of patients with suspected lung cancer and 83.3% (n=10) of those with mediastinal pathology.

The imaging diagnosis in patients with lung and mediastinal tumors can be found in Table 2.

Table 1. Patients' characteristics

	Lung (N=54)	**Mediastinum (N=12)**
	Number	Number
Sex		
Male	44	11
Female	10	1
Age		
Median	57	27.5
Range	min 21- max 72	min 18- max 65
Investigation		
Radiography	54	12
CT	32	10
Tumor size		
median	5.5 cm	15.1 cm
< 5 cm	38	1
6-10 cm	13	4
11-15 cm	3	6
16-20 cm	0	1

Table 2. Radiological description of patients with lung and mediastinal tumors

Radiological conclusion	**Number**
Lung tumors (N=54)	
Primary tumor only	27
Primary tumor and metastasis to the same lung	13
Primary tumor with metastases in the same lung and pleurisy	8
Primary tumor and metastases in the contralateral lung	4
Metastatic pleurisy	1
Malignant pleural mesothelioma	1
Mediastinal tumors (N=12)	
Mediastinal tumor	10
Mediastinal tumor and lymphadenopathy	2

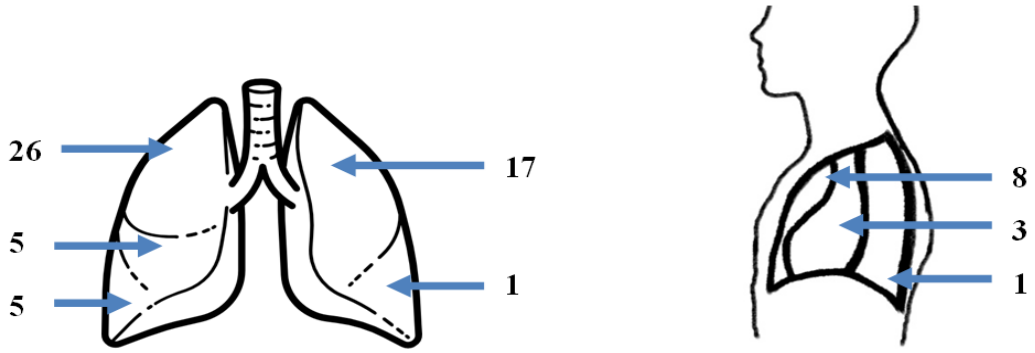

Figure 1. Number of cases corresponding to anatomical location of lung and mediastinal tumors (relative percentage in brackets)

Lung tumors were more frequently located in the superior lobes (79.6%), and most of the mediastinal tumors (66.7%) were in the anterior compartment (see Figure 1).

The transthoracic needle biopsy provided sufficient pathologic material for diagnosing 43 patients (79.6%) with lung tumors. Out of these, 32 cases were identified as lung cancer, the rest were found to be either tuberculosis or pulmonary fibrosis. In the case of mediastinal tumors, the transthoracic biopsy provided a conclusive diagnosis for 10 patients (83.3%) (see Table 3).

Table 3. Morphological diagnosis of lung and mediastinal tumors, respectively

	Number
Lung tumors (N=54)	
Adenocarcinoma	13
Squamous cell carcinoma	11
Tuberculosis	7
Large cell carcinoma	5
Foci of pulmonary fibrosis	4
Small cell carcinoma	3
Inconclusive	11
Mediastinal tumors (N=12)	
Non-Hodgkin's lymphoma	5
Mediastinal lymphoma	3
Hodgkin's lymphoma	2
Inconclusive	2

Lung cancer was identified in 32 (59.3%) of the 54 patients initially diagnosed with lung tumors. The transthoracic biopsy failed to establish a definitive diagnosis in 13 patients. These cases were subjected to further evaluation by the multidisciplinary board. Despite the associated risks, it was determined that a diagnostic thoracotomy was necessary in 6 of these cases. In 7 instances, the circumstances were deemed inoperable. Complications seen after percutaneous transthoracic needle biopsy in lung tumors were reported in 5 cases (9,3%). Among these, pneumothorax was described in 3 patients (5,6%), who all required subsequent pleural cavity drainage. Hemoptysis occurred in 2 patients (3,7%), which was subsequently

stopped by administering hemostatic agents. In patients with mediastinal tumors, pneumothorax was reported in 2 cases (16,7%) following the percutaneous biopsy.

4. Discussion

A significant advantage of this method is the possibility of performing the procedure under only local anesthesia, which is essential for patients suffering from various comorbidities that generally don't allow undergoing general anesthesia. The good results and low rate of adverse events seen in transthoracic percutaneous puncture in our patients are evident.

In our study, for patients considered unfit for more invasive diagnostic procedures, FGTNB established a conclusive diagnosis in 79.6% of lung tumors and 83.3% of mediastinal tumors, with a rate of manageable adverse effects of 9,3% and 16.7% for lung and mediastinal tumors, respectively. Patients with tumors in the superior lung or the anterior area of the mediastinum were more suitable for the procedure, as the approach was more straightforward, and the risk of adverse events was lower.

A cohort study of 100 patients comparing the accuracy, safety, and effective dose (ED) of FGTNB with CT-guided needle lung biopsy (CTNLB) procedures demonstrated that the adequacy rate of was 95%. The overall sensitivity of FGTNB for detecting malignancy was 87%. Overall accuracy was also 87%. The specificity and positive predictive value were 89% and 99%, respectively, but with a pneumothorax complication rate of 25%. FGTNB is faster, taking only 15 minutes (fluoroscopy-guided CT biopsy of lung lesions ranged from 15 to 41 minutes, with a mean of 23.8 min). FGTNB has proven to be a real-time imaging modality and is associated with low radiation dose to the patient and operator. With the use of a multiplanar fluoroscopic unit, it is usually possible to document the correct placement of the needle tip within the lesion, including small lesions (6).

However, another cohort study of 235 patients using CTNLB demonstrated that the overall diagnostic accuracy was 95.4%, with 95.52% sensitivity, 100% specificity. Complications occurred in 51 patients, and the overall complication rate was 21.7%. The most frequent complication was minor pneumothorax with a rate of 19.1% (7).

Other studies have demonstrated that the effectiveness of this method is 86% with radiological guidance and 95% when using CT guidance. When using CT as a guiding method, sufficient pathological material was obtained for cytological examination in 89% of patients and for histological diagnosis in 93% of patients. (8,9).

Over the last few years, improvements in imaging, needles, and procedural techniques have all reduced complication rates. Some rare complications include air embolism and tumor seeding, seen in less than 1% of cases. Factors associated with increased rate of complications include the patient's age, comorbidities, tumor size and location, and the number of punctures performed (10).

The limitations of our study were performing the puncture only with the use of radioscopy, which did not allow us to compare the effectiveness of using CT guidance. We also only compared a relatively small number of patients, and these results generally only apply to patients with severe comorbidities who had contraindications for other, more traditional diagnostic interventions.

5. Conclusions

For patients with lung or mediastinal tumors where obtaining a surgical tissue biopsy is not feasible, and the CT-guided biopsy is not available, the fluoroscopic guided transthoracic biopsy may provide the necessary material for pathologic diagnosis with a satisfactory success rate and relatively low risk of manageable adverse events.

Abbreviations:

CT – Computed Tomography
FGTPB – Fluoroscopic Guided Transthoracic Puncture Biopsy
CTNLB – CT Guided Needle Lung Biopsy

Statements:

Author's contributions: MV, SD, and PC conceived the discussed topic; MV, CP, SD, MA, and MEC drafted the initial paper; MV, MA, MEC, and CC made the final revisions to the final paper.

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

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The Coincidence of *Aspergillus* and Primary Lung Adenocarcinoma. A Case Report and Literature Review

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Abstract

Although infrequent, lung cancer can be disguised by the synchronous presence of a fungal infection, most notably by the *Aspergillus* species. Some cases of incidental adenocarcinoma diagnosed during surgical treatment of pulmonary aspergillosis have been reported, showing just how these fungi can hide more serious, underlying pathology.

This review aims to raise awareness about this occurrence to accelerate the correct etiological diagnosis, establish a timely oncological treatment, and improve the overall morbidity and mortality in lung cancer patients. In addition, we present a rather alluring case of concurrent adenocarcinoma and *Aspergillus* infection to display how these two entities can appear together.

Keywords: *lung cancer, adenocarcinoma, aspergillus, aspergillosis*

Case Reports

1. Introduction

Despite significant advances in detection measures and therapeutical management, primary lung cancer remains the most fatal type of malignancy globally, regardless of gender. The high mortality rate of broncho-pulmonary neoplasia could undoubtedly be attributed to delayed diagnosis, taking into consideration the variety of non-specific symptomatology and imaging appearances (1)(2)(3).

Adenocarcinoma represents the most frequent subtype of lung neoplasia, comprising around 40% of the cases worldwide. It tends to develop within the peripheral parenchyma, thus being more challenging to diagnose by bronchoscopy with biopsy. Moreover, several case reports describing an association between the synchronous presence of cavitary bronchogenic carcinoma and chronic fungal infections, particularly aspergillosis, have been published (4)(5).

Aspergillosis entails a spectrum of different clinical presentations of an infection with a prominent, pervasive, opportunistic type of mold. Symptomatology depends mainly on the

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immunological status of the affected host. The most involved species are represented by *A. fumigatus* and *A. flavus*, affecting different organ systems. Symptoms depend mainly on the primary infection site and route, ranging from the lungs, brain, bones, and skin(6).

Immunocompetent individuals hardly suffer from lung aspergillosis, as innate immunity prevents disease establishment. Previously scarred lung tissue or impaired pulmonary function are predisposing factors for an acute or chronic infection following the inhalation of *Aspergillus* conidia. Hematological cancers are also widely acknowledged risk factors for aspergillosis, as they often manifest through relative neutropenia.

We present a case of lung adenocarcinoma paired with a chronic *Aspergillus* infection, which initially disguised the neoplasia, thus prolonging the diagnosis and initiation of treatment. We also offer a literature review of similar cases to emphasize this relatively infrequent yet critical association (4, 7).

2. Case report

A 54-year-old woman, never-smoker, without any relevant history of acute or chronic lung disease, presented with persistent fever, spasmodic cough, and breathing difficulties that had occurred two weeks prior and worsened despite levofloxacin treatment prescribed by her primary care physician.

There was no history of weight loss or chest pain. The patient's medical record revealed primary hypertension, treated appropriately, thyroidectomy for benign goiter, and a hysterectomy for symptomatic uterine fibroma.

On admission, the patient was pale and febrile (38.5 °Celsius), with a BMI of 24. She was hypotensive and in acute respiratory distress, with frequent dry cough, tachypnoea (30 breaths/minute), and hypoxia (peripheral oxygen saturation of 88% in room air), without any palpable lymphadenopathy. She denied any relevant personal medical and occupational history, including tuberculosis, HIV infection, and exposure to silicates. She also denied any family history of lung disease.

Laboratory findings disclosed an elevated number of leukocytes with a predominance of neutrophils (70%), hypochromic microcytic anemia, thrombocytosis, and elevated inflammatory markers (elevated C-reactive protein, high erythrocyte sedimentation rate and hyperfibrinogenaemia). A COVID-19 antigen test was performed on admission with a negative result. Considering the presumptive diagnosis of an acute pulmonary infection, a chest x-ray was ordered, which showed a single cavitary lesion in the right pulmonary area with a diameter of approximately 4 centimeters (see Figure 1).

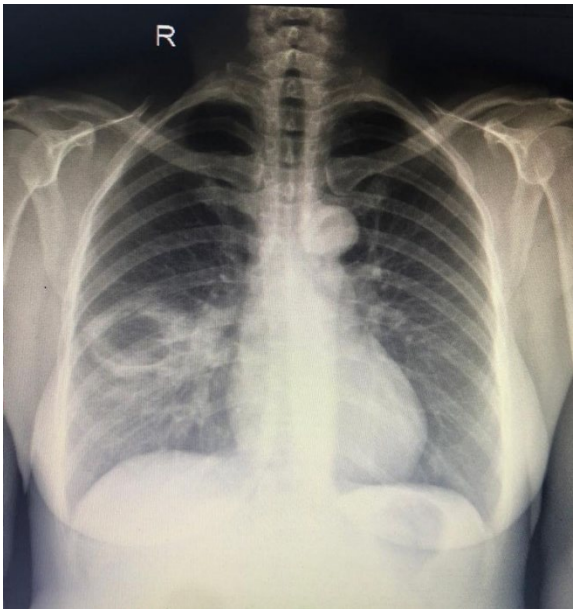

Figure 1. Chest X-ray on admission showed a hyper-transparent circumscribed lesion with a thick, anfractuous contour adjacent to the right pulmonary hilum.

Following the results of her chest x-ray, a chest computed tomography was ordered, which confirmed the cavitary lesion in the apical segment of the right lower lobe. It further described the presence of ground-glass opacities at this level. There was also a minimal pleural effusion on the posterior side of the right hemithorax (12 mm thick), accompanied by bronchiectasis in the same area (see Figure 2). No masses or mediastinal/ hilar lymphadenopathy were described. At this point, antibiotic therapy was changed to ensure broad-spectrum coverage.

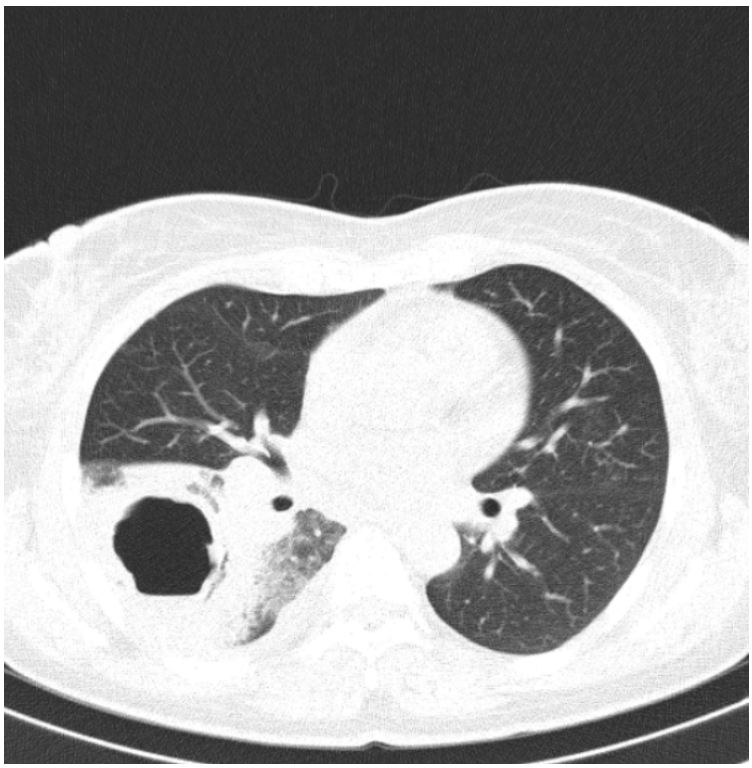

Figure 2. CT scan of the chest showing a cavitary lesion within the lower right lobe surrounded by ground-glass opacities.

Sputum samples were difficult to obtain because of the dry cough, which prompted repeated specimens. Bacterial and fungal cultures, gram stain, and Ziehl-Neelsen stain were all negative. Tuberculosis (TB) infection was ruled out because of the negative result of nucleic acid amplification tests (GeneXpert), negative cultures on the Lowenstein-Jensen medium, and negative interferon-gamma release assays. Concomitant HIV infection was also ruled out because of the absence of HIV-specific antibodies.

Bronchoscopy showed hyperemia of the right lower lobe lining, with associated seromucous secretions, factoring out proliferative lesions. Microscopy examination of the bronchial aspirate showed extracellular Gram-positive diplococci, Gram-negative bacilli, neutrophils, and degraded epithelial cells. Notably, there was no initial bacterial growth on the culture medium. Cytology of the sputum specimen was negative for any atypical cells.

After twenty days of hospitalization and systemic administration of antibiotic therapy, the patient developed an increase in temperature to around 40 degrees Celsius, with general malaise, leukopenia, thrombocytopenia, and a change in cough now with hemoptysis. The cultures from the sputum sample were now positive for colonies of *Aspergillus* spp. In response to these new findings, voriconazole was added to the intravenous treatment regimen. The sputum microbiological cultures were also positive for Methicillin-resistant Staphylococcus aureus (MRSA), *Klebsiella*, and *Pseudomonas aeruginosa*.

After treatment initiation for these pathogens, the patient displayed a favorable clinical evolution, with remission of fever and an expected drop in WBC count and inflammatory markers. Another CT scan of the chest with contrast was performed three months after admission, showing dimensional regression of the cavitary lesion, which measured around 3 cm (see Figure 3).

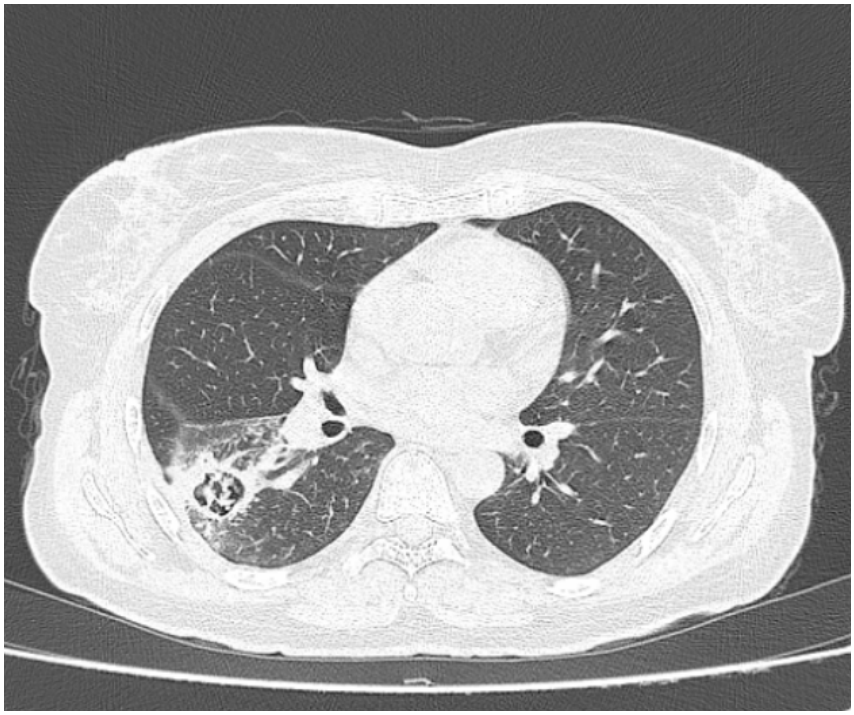

Figure 3. CT scan depicting the evolution of the cavitary lesion after exactly three months of systemic antibiotic therapy.

Following medical treatment, a surgical plan was introduced. A right lower lobectomy was performed, displaying incomplete resolution of the abscess. The histopathological examination of the specimen revealed the presence of bronchiectasis (colonized by dichotomic hyphae identified as *Aspergillus* spp.) and chronic inflammatory infiltrate surrounding the three-centimeter cavity. Alongside this was described fibrosis, granulation tissue, and necrotic tissue, all suggestive of *Aspergillus* colonization. The cavity was identified as an Aspergilloma but was unexpectedly surrounded by areas of poorly differentiated malignant cells, constituting an occult adenocarcinoma. Further immunohistochemical testing confirmed the presence of a primary lung adenocarcinoma.

Since malignancy involvement was not suspected before the surgery, hilar and mediastinal lymph nodes were not removed during the procedure. As a result, lymph node involvement could not be excluded, and post-operatory endobronchial ultrasound was not feasible. Following a multidisciplinary approach, systemic adjuvant chemotherapy for non-small cell lung carcinoma was initiated. The patient is now undergoing adjuvant treatment with Cisplatin/Pemetrexed (Cisplatin 75 mg/m2 day 1, Pemetrexed 500 mg/m2 day 1, every 21 days, for four cycles) for a T2aNxM0 (stage IB) poorly differentiated lung adenocarcinoma.

3. Material & methods

We searched “Google Scholar” and “PubMed” for similar cases of simultaneous occurrence of primary lung adenocarcinoma and *Aspergillus* to assess the similarities and difficulties encountered in establishing a diagnosis. While doing so, we acknowledged that lung

cancer, in general, not necessarily a particular subtype prone to cavitation, can be associated with concomitant *Aspergillus* infection. This enforces our objective of advocating for the meticulous elimination of lung cancer, especially when dealing with previously healthy and immunocompetent individuals newly diagnosed with pulmonary aspergillosis.

Several case reports, mini-reviews, and relevant abstracts have been published. Despite this, it would be beneficial for an entire article to display the relationship between concomitant Aspergillosis and lung cancer. Data from these case reports were notably included and analyzed in one extensive review by Nilsson et al., from 2011 (4), which identified over twelve years three more cases of incidental adenocarcinoma coexisting with an *Aspergillus* infection (see Table 1).

4. Discussion

Upon further review, we have identified eleven other case reports with a positive diagnosis of primary lung adenocarcinoma associated with *Aspergillus* spp., colonization, or invasion (8–17). There is a significantly increased prevalence in men (10:1), with a median age of 59 and a mean age of 57. Seven patients are chronic tobacco users, as opposed to our case. Two case reports (10, 16) provide no data about the patient's smoking history. This could hint that adenocarcinoma co-infected with *Aspergillus* is more prevalent among smoking men.

Lung cancer is more frequently diagnosed among smokers, but this is not the case for the adenocarcinoma subtype, which is notorious for its incidence in non-smokers or never-smokers (2, 18). We believe the link is not necessarily between adenocarcinoma and smoking but between the latter and the co-presence of adenocarcinoma and *Aspergillus*. The cause might be the persistent destruction of alveolar septa and the generation of dilated bullous spaces, which leads to a favorable colonization site for the saprophytic, opportunistic fungi (11).

Table 1. Primary lung adenocarcinoma associated with *Aspergillus* infection (* - the period is unspecified, making pack years impossible to calculate; ** - Only tuberculin intradermal reaction test was positive, along with a cavitary lesion on X-ray situated within the upper right pulmonary lobe)

Author, year	Gender	Age	Pack year	Acute/ subacute/ chronic symptoms	Lesion type	Location	Maximum diameter	TB tests	Presumptive diagnosis	Bronchoscopy
Smahi et al, 2011	M	60	25	Subacute	Cavitary	RUL	45 mm	Negative	Aspergilloma	Negative
Boyd et al, 2012	M	48	32	Subacute	Cavitary	RUL	85 mm	Negative	Pulmonary abscess	Negative
McGregor et al, 1989	M	64	?	Chronic	Cavitary	LUL	45 mm	Negative	Fungal infection/ Carcinoma	Negative
Itano et al, 2005	M	77	56	Asymptomatic	Opacity	RUL	17 mm	Negative	Carcinoma	-
Saleh et al, 2008	M	54	Smoker	Subacute	Cavitary	RUL	15 mm	Negative	Aspergilloma	Negative
Mays et al, 1966	M	45	50	Chronic	Cavitary	RUL	25 mm	Negative**	Tuberculosis	-
El Hage and Fagel, 2020	F	82	Heavy smoker	Acute	Opacity	RUL	-	Negative	ABPA	Adenocarcinoma +Aspergillus
Marcelis et al, 1981	M	38	1 pack a day*	Unspecified	Cavitary	RUL	30 mm	Negative	Carcinoma	Negative
Fujita et al, 2018	M	82	?	Asymptomatic	Cavitary	LLL	-	Negative	Chronic progressive pulmonary aspergillosis	Adenocarcinoma +Aspergillus
Yoshitomi et al, 2000	M	60	0	Acute	Opacity (atelectasis)	LLL	-	-	Carcinoma	Adenocarcinoma +Aspergillus
Yoshitomi et al, 2000	M	53	0	Asymptomatic	Opacity	LUL	65 mm	-	Carcinoma	Adenocarcinoma +Aspergillus
Our case	F	54	0	Acute	Cavitary	RLL	40 mm	Negative	Pulmonary abscess	Negative

One patient presented with dizziness, which was initially interpreted as acute labyrinthitis. The same patient reported a brownish productive cough for over 20 years and never sought treatment. (13). The rest of the patients presented with various subacute and chronic symptoms, including productive cough (8, 9, 12, 14, 17), hemoptysis (8–10, 12, 15), unintentional weight loss (12, 13), while concomitantly displaying thoracic and right arm pain, alongside generalized urticarial rash (15). Three patients were utterly asymptomatic (11, 16, 17).

Productive cough, hemoptysis, and weight loss are superposable clinical features of a potential neoplasia. In this case, even though paraclinical tests strongly suggest a pulmonary fungal infection, we must emphasize that ruling out concomitant cancer must be prioritized (7, 19). However, our patient presented with acute symptoms, leukocytosis, and systemic inflammatory syndrome. The initially negative bacterial and fungal cultures, undetectable hilar and mediastinal lymphadenopathy, and pulmonary mass led to the presumptive diagnosis of a pulmonary abscess. This was also the case for another patient (9) who presented with fever, hemoptysis, and subacute productive cough for five weeks.

Early diagnosis for some of the patients (8, 12, 13, 16) was “Aspergilloma,” mainly due to the characteristic signs on chest radiography and tomography, showing the distinct air-crescent sign (20). One patient (14) presented with branching opacities, considered specific for allergic broncho-pulmonary aspergillosis (ABPA). These patients showed no paraclinical disease resolution despite administration of systemic corticosteroids, antifungal treatment, and favorable clinical progression. One patient (11) who presented with an opacity rather than a cavity on radiographic imaging had a preliminary diagnosis of cancer, confirmed by histopathological examination of the lung tissue.

All the other patients, including ours that initially presented with a cavitary lesion on chest x-ray or CT had no initial suspicion of malignancy until biopsy and histopathologic exam. Considering the positive outcomes of the Mantoux test, despite negative cultures for acid-fast bacilli, one patient (13) was initially diagnosed with pulmonary tuberculosis and subsequently underwent tuberculostatic treatment.

The patient who presented with thoracic pain referring to his right arm (15) had a strong suspicion of an excavated tumor colonized with *Aspergillus* from the beginning, which didn’t show common aspects on shoulder x-ray, electromyography, alongside bone, cerebral, and hepatic scintigraphy. In other words, only four out of twelve (33,33%) early diagnoses were correct based solely on clinical presentation and imaging. This shows the importance of keeping concomitant fungal infections and malignancies high on the differential.

Regarding extensive tests for the detection of *Aspergillus*, four out of twelve patients had relevant bloodwork requested: the antifungal antibodies level was tested in three patients, one of which had positive serology for *Aspergillus*—the other patient presented with an elevated galactomannan (GM) antigen level, which is specific for aspergillosis.

Eight out of twelve (66%) patients presented with a cavitary lesion initially, possibly suggesting that over half of the adenocarcinoma was excavated, providing a favorable environment for germinating *Aspergillus* conidia into hyphae. Another theory is that the concurrent fungal infection with a pre-existent adenocarcinoma could have led to tumoral cavitation, as suggested by Nilsson et al. This could be because of the fungi's secretion of specific lytic enzymes (4), creating further cavitation of the lung parenchyma.

Five of these cavities were first diagnosed as Aspergillomas despite the normal immunological status of the hosts and lack of pre-existing pulmonary disease. The hyper-transparent lesions were predominantly within the right upper pulmonary lobe (7/12). In contrast, two were found in the left lower lobe. There is a well-known predilection of *Aspergillus* to invade the upper pulmonary lobes, meaning that right and left upper lobe cavities were strongly compatible with a diagnosis of Aspergilloma, tuberculous hole, or both, although the latter being less probable because of the absence of risk factors and negative tests for *Mycobacterium Tuberculosis*. However, bronchial carcinomas occur more frequently in the upper lobes (13), complicating the differential diagnosis even fur-

ther in the absence of a mass or lymphadenopathy. *Aspergillus* was masking an underlying neoplasia in nine out of twelve patients.

The average diameter of the cavitary lesions was approximately 40 mm, with a minimum value of 15 mm and a maximum of 85 mm. Every patient in this study underwent diagnostic bronchoscopy, which identified both *Aspergillus* and atypical cellularity in one-third of the patients. Moreover, transbronchial and CT-guided biopsies were also performed, which were normal. Consequently, this led to a missed initial preoperative lung cancer diagnosis in most patients.

A definitive diagnosis was established by assessing the pathology reports from the surgical biopsy specimen. The histopathological report that belonged to our case described a fungus ball surrounded by necrotic and granular tissue, along with chronic inflammatory infiltrates and islets of atypical cells, constituting poorly differentiated adenocarcinoma. The presence of hyphae was described inside the cavity, confirming the pre-emptive diagnosis of Aspergilloma. Seven other cases (9, 10, 12–14, 17) presented with necrotic tissue on their biopsy examination. One of them disclosed (10) foci of bacterial proliferation and exudate, in addition to the dichotomic hyphae.

In contrast, another patient's cavity (11) was lined by bronchiolar epithelium, which suggested bronchiolar dilation near the atypical glandular and epithelial cells with a high mitotic index. One patient's (12) pathological exam revealed central necrosis of the adenocarcinoma, populated by fragmented fungal filaments. Regarding prognosis and tumoral grading, almost all adenocarcinomas were poorly differentiated, which generally implies a poor prognosis compared to a well-differentiated cancer. (21).

5. Conclusions

The case we described of an occult adenocarcinoma, initially hidden by a nidus of chronic fungal infection, was fascinating. Her initial lack of response to treatment showcased the importance of always suspecting concomitant pathologies, especially in patients unresponsive to suspected disease treatment guidelines.

Three months of systemic antibiotic and antifungal medication administration without clinical improvement led to the surgical excision of the affected pulmonary lobe and subsequent histopathological analysis. As an adenocarcinoma was not initially suspected, it only further complicated oncologic management after the fact, as the surgical treatment was thought to be only for the unresponsive *Aspergillus* infection.

This case displays one of many examples that could have been managed better if clinical suspicion of concomitant fungal infection and lung cancer remained high. Even in immunocompetent patients, it remains vital to emphasize the importance of a possible underlying proliferative process in a preliminary diagnosis of pulmonary Aspergillosis.

List of abbreviations:

ABPA – Allergic broncho-pulmonary aspergillosis
BMI – Body mass index
COVID-19 – Coronavirus disease 2019
CT – Computed Tomography
HIV – Human immunodeficiency virus
MRSA – Methicillin-resistant Staphylococcus aureus
TB – Tuberculosis
WBC – White blood cell

Statements:

Authors' contributions: MIL and IMS conceived and planned the analysis. MIL, CMO and CN contributed to the interpretation of the results. MIL took the lead in writing the manuscript. CN and CMO made the final approval. All authors provided critical feedback and helped shape the research, analysis and manuscript

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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In Vivo Lens Dosimetry in a Case of En Face Electron Adjuvant Radiotherapy for Cutaneous Nasal Bridge Basal Cell Carcinoma: A Case Report

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Abstract

Radiation therapy represents one of the main treatment modalities for basal cell carcinoma (BCC), the most common type of skin cancer. The proximity of organs at risk (OARs) increases the risk of side effects. Treatment planning system (TPS) estimates the absorbed dose, but the real value can be determined only by in vivo dosimetry.

We measured the absorbed dose at the lenses' level in a case who received electron irradiation for a resected BCC with positive microscopic margins, located at the bridge of the nose. The thermoluminescent eye lens dosimeters (TLD) were placed under the lead protections. We compared the measured dose with the values estimated by TPS.

The treatment involved delivering 50 Gy in 25 fractions. A Monaco 5.11 Treatment Planning System (TPS) was used to plan treatment with a 9 MeV electron field and a 10x10 cm applicator at a 100 cm Source-to-Skin Distance (SSD). Customized lead layers and circular lead blocks were used for protection.

The TPS estimated maximum doses of 5.87 Gy for the left lens, and 2.70 Gy for the right lens, respectively. After measuring the doses for the first three fractions by TLD, we calculated that maximum dose for the left lens would get to 0.55 Gy, and to 0.30 Gy for the right lens.

In this case report we show that irradiation for a BCC localised at the bridge of the nose is possible with proper shielding and can be safely delivered, without exposing the patient to long-term side effects.

Keywords: *eye shield, case report, lead protection, electron radiotherapy, basal cell carcinoma*

Case Reports

1. Introduction

BCC is a skin cancer type that appears most often on areas of skin exposed to the sun, such as the face (1). BCC often looks like a brown or glossy black bump and has a rolled border. This type of cancer requires unique treatment planning, a challenge for the medical personnel. The available treatment options are variable and can include cryotherapy, surgical excision,

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radiation therapy (RT), and topical agents, or often a combination of these approaches (2,3).

2. Case Presentation

We present the case of a patient, diagnosed during COVID-19 restrictions with BCC localised at the bridge of the nose region resected with positive R1 margins (Figure 1). The histopathological report described the BCC lesion on an irregular skin flap with a size of 20 x 17 mm. We concluded that the lesion infiltrated the skin to the deep dermis, having a thickness of 3 mm, and also infiltrated the edge of lateral and deep surgical excision.The objective of the study was to measure and compare the calculated doses to the lenses from the TPS with the received dose during the treatment, emphasising patient safety as a core value of radiotherapy.

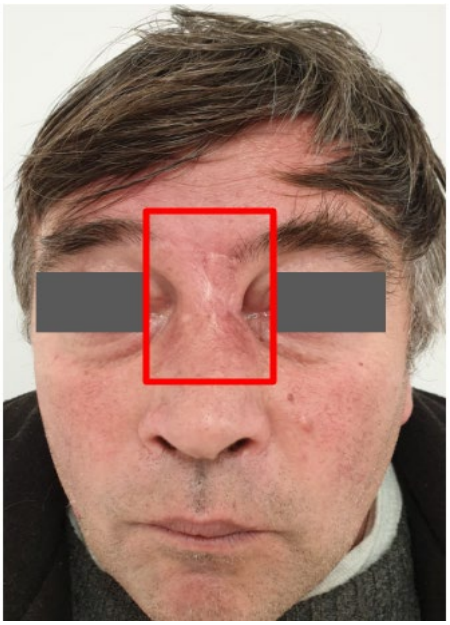

Figure 1. Clinical presentation – image after surgery

3. Contouring and Planning

A computed tomography (CT) scan used for treatment planning was made in supine position, and for immobilisation, we used a 5-point thermoplastic mask. The mask was removed at the nose bridge region for optimal unobstructed irradiation with electron beams. We obtained CT images of the head, acquired using a Siemens CT Simulator. The slice thickness was 3 mm with coverage of all critical organs from the interest zone (see below). The thermoplastic mask was a Green S-type open EM Head Mask with AccuPerf, with a 3.2 mm thickness, which we heated in a water bath at 70 ℃. The mask material becomes mouldable when thoroughly warm, allowing us to fit it perfectly to the patient's face. Once the mask cools, it becomes rigid and highly durable (4,5).

The patient’s outline contour was created by the auto-contouring tools from the TPS, and a radiation oncologist performed the target volume and the organs at risk (OARs) contour tracing. We created clinical target volume (CTV) including the nose bridge region, according to the preoperative description of the lesion and pathology report with the addition of a 1.5 cm margin to the tumour bed (6). We created the planning target volume (PTV) with 0.5 cm margins from the CTV. We considered the following structures as OARs: brain, brain stem, left and right eye, hypophysis, left and right lacrimal gland, left and right lens, optic chiasm, left and right optic nerve, left and right retina, and the spinal cord. As part of the contouring, the physicist had the responsibility to create virtual shielding structures that had the same characteristics as the actual physical ones used during the treatment delivery.

After careful consideration of different treatment options, brachytherapy, external RT with kV beam, electron beam or photon, available in our clinic or at different institution, we have reached a common decision with the patient, and we have chosen a 3D-CRT en face electron irradiation approach. We argued for an electron beam irradiation technique because it is characterised by a rapid dose falloff at a depth below the skin surface, having little radiation exposure beyond a defined depth (6). Considering the localisation of the tumour we decided to deliver a dose of 50Gy in 25 fractions. In this conventional planning technique, we used an anterior beam, with lead protection of the OARs from these regions and eye shields. The lead protection and the eye shields were virtually simulated according to the ones which were used during the treatment The plan calculation was realised on Monaco 5.11treatment planning system (TPS) with

Monte Carlo calculation algorithm. The used energy was 9 MeV, chosen due to the depth of the target, with a gantry angulation of 345 degrees and a couch rotation of 90 degrees. The applicator size was set to 10 x 10 cm, the SSD was 100 cm, and the plan prescription was in depth of beams at 2.5cm （Figure 2a-c). To protect the critical structures, we placed 2 customised layers of 0.3cm lead protection on the applicator and 2 additional single-layer circular blocks of lead on the eyes (similar in size and shape to TPS-created structure (Figure 2d-*f*).

We measured the equivalent dose with two TLD-Hp(3)-type eye lens dosimeters, which were positioned under the orbital lead protections (7). For treating the PTV, we set the objective that the 80% of the tumoral volume (V80%) of the dose should cover a minimum of 95% of the target volume (8), and the dose for the OARs should be as low as possible (Table 1).

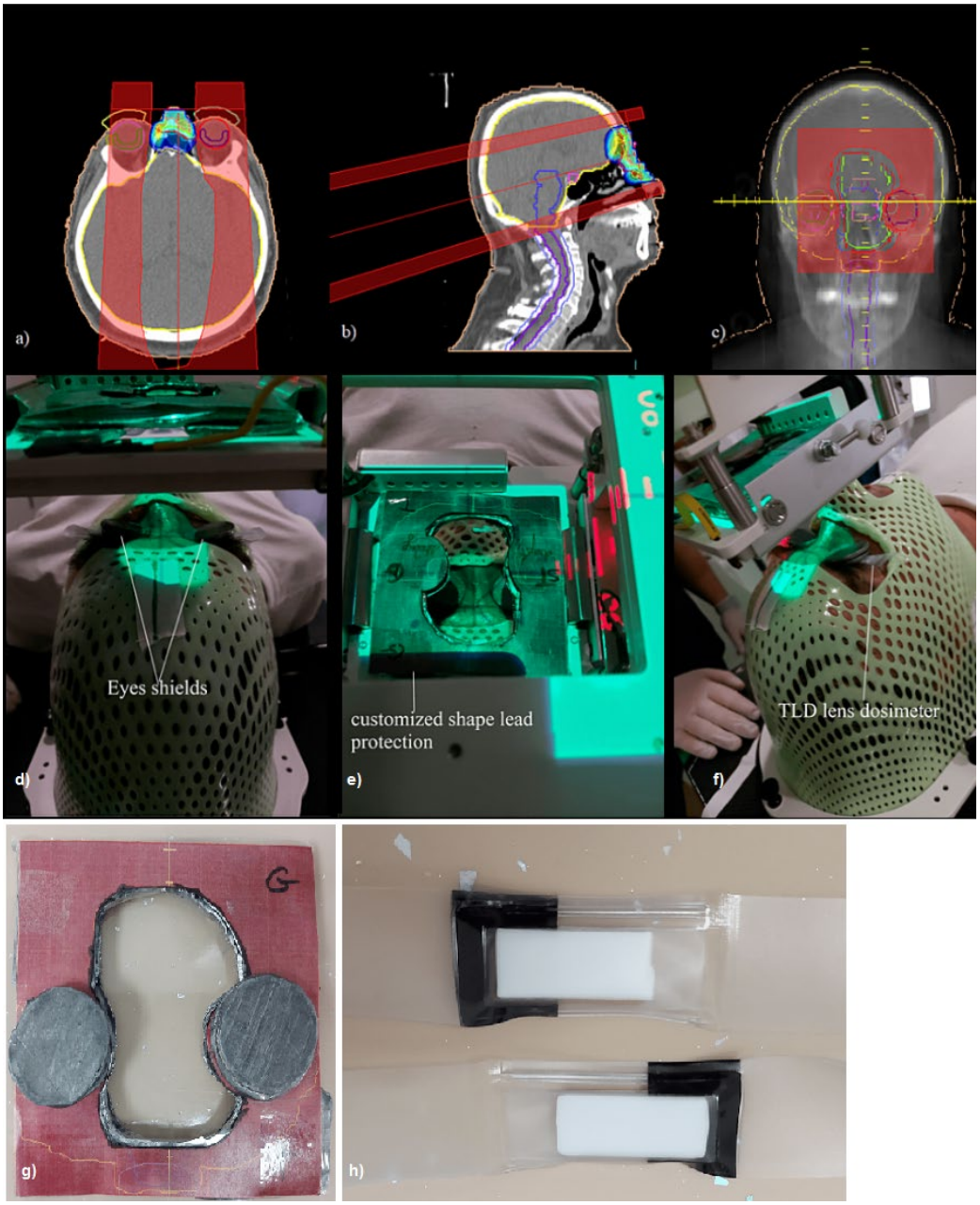

Figure 2. Beam's Eye view (BEV): a) transversal plane, b) sagittal plane, c) frontal plane imagines, d-f) Patient set-up during the treatment delivery with personalized lead protection for the eyes, g)Customized shape lead protection with circular blocks for eyes h) Termoluminescent dosimeters (TLD) Hp(3)

4. Results

Following the evaluation of the target volume, we obtained PTV 50 Gy coverage of 98.11%. The maximum dose on the plan was 70.74 Gy, which is equivalent to a maximum of 141.48%. We had a volume of 0.74 cm^3 (cc), which received a dose of 60 Gy (120%). For a more accurate evaluation, we developed a treatment plan that involved the delivery dose of 60 Gy. This plan showed no significant improvement in terms of either the coverage of the PTV or the OARs (Table 1).

Table 1: Dose constraint compliance for OARs and dose comparison between the 50 Gy and 60 Gy RT plans in case of a BCC irradiation

Goal or Dose constraints		60 Gy/30 fr	50 Gy/25 fr
PTV V80		95.50%	98.11%
PTV V85%		92.69%	96.43%
PTV V90%		88.52 %	93.42%
PTV V95%		81.87%	90.05%
Dmax		131.70% (79.027 Gy)	141.4% (70.738 Gy)
Lens Left	Dmax<7Gy	6.561 Gy	5.873 Gy
Lens Right		3.018 Gy	2.701 Gy
Retina Left	Dmax < 45 Gy (50 Gy)	34.016 Gy	30.448 Gy
Retina Right	Dmax < 45 Gy (50 Gy)	23.123 Gy	20.698 Gy
Eye Left Dmax	Dmax < 50 Gy	37.188 Gy	33.287 Gy
Eye Right Dmax	Dmax < 50 Gy	27.679 Gy	24.776 Gy
Optic Nerve Left	Dmax < 55 Gy (3%)	23.123 Gy	20.698 Gy
	54 Gy < 0.01 cc	18.165 Gy	16.165 Gy
Optic Nerve Right	Dmax < 55 Gy (3%)	14.395 Gy	12.885 Gy
	54 Gy < 0.01 cc	10.455 Gy	9.355 Gy
Optic Chiasm	Dmax < 55 Gy (3%)	2.999 Gy	2.684 Gy
	54Gy <0.01 cc	1.902 Gy	1.702 Gy
Brain	Dmax < 68 Gy	67.764 Gy	60.656 Gy
	60 Gy < 1 cc	62.627 Gy	56.058 Gy
Brain stem	Dmax < 54 Gy (59 Gy)	0.882 Gy	0.79 Gy
	54 Gy < 0.1 cc	0.753 Gy	0.674 Gy
Hypophysis Dmax	Dmax < 50 Gy	1.944 Gy	1.74 Gy
Spinal Cord Dmax	Dmax < 45 Gy	0.398 Gy	0.363 Gy

**BCC – basal cell carcinoma, OAR – organ at risk, RT – radiation therapy, Gy – Gray, measurement unit, Fr – fraction, PTV – Planning target volume*

Evaluating the conformity index (CI) and the homogeneity index (HI) for this setting, we obtained the values HI = 0.37 and CI = 1.01 for the first plan (where we planned to deliver 50 Gy in 25 fractions) and HI = 0.38 and CI = 0.90 for the second plan (where we planned to deliver 60 Gy in 30 fractions).

For evaluation of the treatment plan, we used DVH parameters. (Table 1). Because of better coverage and the novel protection approach we were using; we chose the more conservative approach of 50 Gy/25 fraction (fr). We delivered a total of 253.84 MUs. For in vivo dosimetry we used 2 TLD lens dosimeters, which were placed under the eye shielding (Figure *2d)-f)*). We measured the doses for 3 consecutive days followed by the mathematical interpretation of the results. We obtained absorbed doses for both lenses around 10 times smaller than those calculated through the TPS (Table 2).

Table 2. Dose measurement results and conversion from equivalent dose to absorbed dose (1 mSv= 0.001 Gy)

	Measured Doses			Estimated Doses (TPS)
Lens	**mSv/ fr**	**Gy/ fr**	**Total 50 Gy/25 fr**	**Total 50 Gy/25 fr**
Left	12.67	0.01267	0.317	2.701
Right	22.24	0.02224	0.556	5.873

**TPS – Treatment Planning System, mSV – millisievert, Gy – Gray, fr – fraction*

5. Follow-up

We continuously evaluated the patient's condition during the treatment, noting expected adverse events for RT on the skin and good responses to topical treatments for radiation dermatitis. We instructed the patient to perform periodic routine check-ups both at surgical and radiation oncology departments. At the first follow-up (3 months post-RT), late side-effects of RT were hyperpigmentation G1, skin dryness G1, pruritus G1, skin induration G2 and hot flashes G1 in the treated area (Common Terminology Criteria for Adverse Events - CTCAE v5 grading). Imaging via regular CT or magnetic resonance imaging (MRI) imaging with contrast, to monitor the head and neck region for potential regional recurrence, was recommended, this likewise showing patient as disease-free.

6. Discussion

Here, we report a case where we applied a treatment plan to a delicate anatomical region. We applied it with a linear accelerator commissioned to electron beam therapy, a therapy we consider a potentially viable strategy in BBC irradiation to improve treatment compliance and reduce costs. Because of distinct planning limitations owing to the variability of resources facilities equipped with either contact RT, brachytherapy, or 3D-printed bolus solutions available for RT departments, it is challenging to suggest a one-size-fits-all radiotherapeutic guideline for BBC treatment of the nose.

In the planning phase we considered alternative treatment options, with all specialities of the RT staff (physician, physicist, and RT technician) giving input. We took into consideration the use of orthovoltage, brachytherapy, and the application of bolus materials. We considered the possibility of using bolus materials impractical because of the anatomical curvature of the nasal region and the possible variability with daily reproducibility over several fractions.

It has been documented that the COVID-19 pandemic increased anxiety among cancer patients with high levels of distress calling for a multidisciplinary perspective. Likewise, patients' mobility and perception of risk has been affected during the pandemic (12). Taking these into account we could not consider the option of brachytherapy and orthovoltage (available at distant medical facilities) because of poor accessibility and logistical reasons, the patient having informed us of these limitations beforehand. Thus, we consider direct electron beam irradiation an optimal compromise for this patient.

In the setting of adjuvant RT for an R1 resection of BCC, the administered dose should approach 60 Gy/30 fr (8). In the multidisciplinary meeting, because of anatomical particular-

ities of the target volume, we reached a compromise to deliver a dose of 50 Gy in 25 fractions. Upon slice-by-slice review of the RT plan we noted that the hot spots reaching ≥ 60 Gy were in the positive margin region (towards the eyes) in corroboration with the postoperative pathological report. Hypofractionation schemes have also been proposed but due to lack of experience with higher dose per fraction with electron RT the choice was made to continue with a traditional 2Gy/fr approach.

Among the techniques we have in our department, we considered the most optimal to be electron beam therapy, even when taking into account its limitations compared to other irradiation methods. Limitations of our technique include the uncertainty of beam homogeneity after entry because of the lack of flat surfaces, creation of hot spots and daily reproducibility variations. We tried to address these shortcomings by making sure that no thermoplastic mask material was interposed between the skin and the beam, as well as by using double lead shielding on both the applicator and on the eyes. As a technique, we consider our solution a straightforward and treatment which requires additional verification of compliance for each step according to guideline recommendations, by the physicist and the attending physician (6,9,10). We guaranteed our set-up reproducibility by a detailed description of immobilisation devices used, mapped photographs for RT technologists and participation of the entire treatment team every second and third fraction. In a similar study to ours Wang et al (11) conducted a study in which they measured the dose of the eye by using a 3D-printed bolus eye shield, concluded with similar results with ours. The difference between the two studies was the fact that the wax bolus permitted to have a simulation CT scan of the surface, while the lead protection used in our approach would lead to significant artifacts.

7. Conclusions

To our knowledge, this report is among the first to describe en face adjuvant electron radiotherapy treatment in which lead protection was used for shielding the eyes. With the aforementioned impediments, we consider that the treatment has been safely delivered under strict dosimetric supervision and represents a cost-effective alternative for cases where other options are logistically inopportune for the patient, made even more difficult by local COVID-19 restrictions. With the possibility of a relatively easy reproducibility of our approach and the accumulated experience, we feel confident about potentially escalating doses, applying hypofractionated schedules, and including a larger number of patients in the form a prospective registry of en face electron radiotherapy.

Abbreviations:

BCC – basal cell carcinoma
Gy – Gray, measurement unit
TPS – treatment planning system
SSD – Source - surface distance
RT – radiation therapy
CT – computed tomography
OAR – organ at risk
CTV – clinical target volume
PTV – Planning target volume
3D-CRT – 3D conformational radiation therapy
CI – Conformity index
HI – Heterogeneity index
DVH – dose volume histogram
MU – Monitor Unit
Fr – fraction

Statements:

Authors' contributions: Conceptualization: GS, KV, DP; Investigation and Validation: GS, KV; Writing- Original Draft preparation: GS, DP; Writing - Review & Editing: GS, DP, ZB; Visualization: GS, DP; Project Administration: GS, DP; Supervision: ZB, DP; Final approval of manuscript: GS, DP, KV, ZB.

Consent for publication: As first author, I confirm that the manuscript has been read and approved by all authors and that the order of authors listed in the manuscript has been approved by all of us.

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Current Perspectives on the Evolving Role of Radiation Therapists – Highlights from ESTRO23

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Abstract

Radiation therapists, also called Therapeutic Radiographers or Radiation therapy technologists (RTTs) are uniquely placed within the radiotherapy (RT) multidisciplinary team, as the use the technology and deliver the treatment but they are also patient focused. The implementation of technological advancements such as image-guided radiotherapy (IGRT), adaptive radiotherapy (ART), surface-guided radiotherapy (SGRT), and AI-based solutions necessitates acquiring new skills and competences. RTTs' daily involvement in patient's treatment allows the assessment of their needs and perspectives. Implementing a holistic approach to patients' comfort during RT, beyond positioning and immobilisation, reduces anxiety and increases compliance. The RTTs offer valuable feedback regarding potential challenges or improvements after new technology or new procedures' implementation, essential for the enhancement of these innovations. Complex educational interventions focused on modern technology, communication and research competencies are required so that RTTs can optimally fulfil their essential role in cancer care.

Keywords: *RTT, radiotherapy, IGRT, ART, SGRT, immobilisation, positioning, comfort, communication*

Viewpoint

1. Introduction

Previously, it was believed that about half of all cancer patients would undergo radiotherapy (RT) at some stage of their treatment journey. However, the scope and applications of RT are currently broadening (1). Clinical oncologists make the treatment indication, while the daily administration is the responsibility of Therapeutic Radiographers/ Radiation Therapist, hereafter referred to as Radiation Therapy Technologists (RTTs). The RTTs are the only professionals who can legally turn the beam on and deliver the treatment, but their responsibilities extend beyond machine operation. They represent a specialised branch of allied health professions demanding ad-

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vanced tertiary education and substantial clinical experience.

In certain countries, such as the UK, the RTTs are the exclusive group to pursue dedicated undergraduate studies in radiotherapy and oncology. Nonetheless, there are educational discrepancies across Europe. The care of radiotherapy patients is a collaborative effort involving various professionals from the initial diagnosis through treatment planning, delivery, on-treatment monitoring and post-treatment phase. However, RTTs have the unique privilege of engaging with patients daily throughout their treatment journey. This places them at the forefront of cancer care, uniquely positioned to provide consistent patient support and ongoing care.

Radiation oncology is an evolving medical field marked by technological progress, particularly in computer science and machine learning. RTTs are adapting to changes in treatment delivery methods and need to continuously update their knowledge and skills (2).

This manuscript represents a perspective on the evolving role of RTTs in the context of current changes in technology and holistic patient approach, including some highlights from the European Society for Therapeutic Radiology and Oncology (ESTRO) annual meeting.

2. Recent developments and their impact

2.1. Evolution of RTTs' role

The central theme of the ESTRO congress in 2023 was "From Innovation to Action", sparking in-depth discussions encompassing numerous aspects of incorporating AI into clinical radiotherapy practices. The possibility that Artificial Intelligence (AI) will replace specific tasks traditionally performed by RTTs remains a topic of active deliberation.

AI can improve the delivery of RT in many of the treatment stages: contouring of the organs at risk and target volumes, dose calculation and quality assurance. Specifically trained AI algorithms could also assist in automatic patient setup and positioning by analyzing imaging data or continuously monitor patients during treatment, analyzing changes in anatomy and suggesting adapted treatment plans. The AI could also assist the RTTs in recommending patients personalized education materials for improving patients' understanding and compliance. Being able to analyze large volumes of patient data, AI has the potential to contribute to workflow optimisation and subsequently a better resources utilisation. It can also contribute to research, by identifying patterns, treatment response and outcomes, which could determine changes in the current approaches. Rather than a replacement, it is much more probable that AI will function as a complementary tool, aiming to streamline and facilitate the responsibilities of RTTs, similar to an additional team member. Therefore, it becomes important to provide the RTTs the appropriate education on AI and involve them in discussion in this topic. According to a recent survey assessing the Irish RTTs' opinion on AI, almost half of the respondents anticipated reducing staff levels with AI, and a similar percentage already used AI-based solutions. However, 70.6% felt AI would be positive for the patients, and 94% favoured AI implementation (3).

The optimisation of clinical workflows and ensuring efficiency in service delivery relies on collaboration between RTTs, treatment planning system vendors, and manufacturers of treatment and imaging technologies. As technological systems advance, a continuous educational framework is needed. Empowering therapists to thrive in this dynamic environment requires active participation in research endeavours, including a broader engagement in domains such as AI and Image Guided Adaptive RT.

Within the clinical decision-making process, RTTs should possess an innate ability to make independent determinations regarding immobilisation selection and the acquisition of pre-treatment scans. Integrating these emerging subjects into professional education reflects the ever-evolving landscape of radiotherapy (4).

2.2. Image Guided Radiotherapy and Adaptive Radiotherapy

In slightly over a decade, Image Guided Radiotherapy (IGRT) became part of the current practice (5). Image quality increased and made it possible to visualise the targets and

organs at risk more precisely. Bony anatomical surface landmarks positioning has been replaced by kV and MV images, cone-beam CT and more recently by real-time MRI, 4D CT, use of fiducial markers or surface-guided systems (6).

Professional Societies' joint efforts resulted in updated recommendations clearly stating the RTTs role as multidisciplinary team members and the need for adequate training and clear procedures. “On target 2”, for example, is a report that provides updated recommendations for the application of image-guided radiotherapy and to enable future implementation of four-dimensional (4D) adaptive radiotherapy. The main recommendations refer to many practical aspects, such as the integrative approach of the entire patent pathway and adapted process in terms of imaging frequency and dose. The importance of effective immobilisation is also underlined, as well as the necessity of place-specific protocols. Routine prospective data collection and analysis is considered essential to identify systematic or random errors and the most appropriate values for margins. Participation in clinical trials is encouraged to develop and implement IGRT protocols (7).

Adaptive Radiotherapy (ART), a recent development, implies changing the RT plan as a result of changes in the target position, due to tumour volume variations, weight loss or intrafractional movements, as organs’ internal motion (8). There are two strategies for adapting the treatment plan. One implies choosing for a “library of plans”, approximating the best fit of planning target volumes (PTV), based on an onboard cone beam CT (CBCT). Another option is the daily adaptation of the treatment plan based on CBCT or MR, with the patient on the treatment couch, also named online adaptive radiotherapy (9). Reviewing, editing and accepting the contours for target volumes and organs at risk is traditionally the responsibility of physicians. However, while more patients receive online ART, especially with the increased use of hypofractionated schedules, there is a shift towards an RTT-led workflow (10). Two reports from the Netherlands showed that a comprehensive training program allowed RTTs to independently treat prostate cancer patients. One of the programs allowed the delivering of 1000 fractions with only 5 requests of physician’s intervention (11). In the the second one, 94% of the 150 RTTs’ contours for MRI guided ART were clinically acceptable (12).

However, these enhanced treatment modalities have specific considerations: prolonged appointment times, the essential involvement of the entire multidisciplinary team (including radiation oncologists and physicists), and modified patient expectations. Patients must be informed before treatment starts regarding the treatment process (involving various personnel in the workflow) and their roles (such as engaging in training exercises for controlled breathing). Therapists can provide written materials, organise informative sessions, or develop radiotherapy-related videos/presentations to facilitate comprehension. The primary goal of patient education revolves around mitigating anxiety or concerns while enhancing their understanding of the procedure.

Patient selection criteria are integral to the ART process, as careful screening assesses patient performance, compliance and potential contraindications. Self-report measures can be used to predict the risk of RT session disruption due to anxiety (13). Patient positioning is directly impacting ART. Since real-time adaptive treatment sessions inherently require more time than standard RT fractions, RTTs must ascertain the patient's capability to sustain stable and comfortable positions to ensure minimal patient movement during treatment. Effective communication with patients is required throughout the adaptive RT sessions, so the RTT must ensure the technical functionality of intercom systems for in-treatment communication and the development of communication skills needed in patient interaction (14).

Accurate collection of data regarding treatment and patient’s feedback It is the responsibility of the RTTs, who need to collect this information in a way that reflects the patients point of view but also has the also scientific rigor, so the data can be analysed. Therefore RTTs need a certain amount of research education so that they can appropriately undertake such projects. RTTs’ involvement in

research activities should be encouraged and supported by educational and practical interventions. for the benefit of the patients and the multidisciplinary team. As discussed also during the ESTRO 2023 session, “Education is the RTTs superpower”.

2.3. Surface Guided Radiotherapy (SGRT)

Over the past few years, the clinical utilisation of SGRT has gained widespread adoption, encompassing various techniques and treatment sites. This technology, relying on optical surface scanning, has been integrated into clinical protocols, necessitating comprehensive guidance for its implementation across diverse treatment scenarios.

An international survey on current clinical practice published in 2022 gathered data from 278 institutions and reported that half were using SGRT. The main clinical application was patient positioning, motion management, and deep inspiration breath hold. The perceived drawbacks to broader application were financial, logistic and insufficient data on clinical value (15). Recognising this need, ESTRO has provided guidelines that involve staff member roles and responsibilities. The ESTRO-ACROP guidelines also address procedure challenges and outline potential system failure scenarios. Institutions implementing SGR are advised to follow the guidelines to ensure the proficiency of each staff member in every step of the workflow (16).

An ESTRO 2023 presentation by Filipe Moura on the clinical implementation of SGRT presented results from the survey, the main current recommendations and some interesting data on system capabilities. Position changes of 1 mm or 1 degree can be identified using SGRT, and the possibility of a thermal map also exists for some systems. Templates and adapted protocols for different anatomic sites are needed for optimising the workflow. While daily imaging remains essential, SGRT has the potential to expedite image registration and reduce the need for frequent imaging, ultimately streamlining the treatment process (17).

Since RTTs are pivotal in patient preparation, positioning, monitoring, and treatment administration, training sessions and continuous education are indispensable to avert potential errors and suboptimal technology usage. Regular quality assurance tests, from daily or weekly checks to monthly or annual evaluations, uphold the system's integrity. While daily imaging remains essential, SGRT has the potential to expedite image registration and reduce the need for frequent imaging, ultimately streamlining the treatment process (18).

The field is persistently advancing towards novel methods of assessing not only precise positioning but also the surfaces exposed to radiation during treatment. A recent promising breakthrough involves the utilization of a time-gated three-channel camera, which captures the broadband light emitted due to the Cherenkov Effect. (19).

2.4. Positioning, immobilisation and patient comfort

Positioning and immobilisation of patients are crucial for reproducible and accurate delivery of radiotherapy to ensure tumour control and avoid healthy tissue toxicity. An essential role in position holding and compliance with treatment plans in radiotherapy is patient comfort.

A systematic review by Goldsworthy *et al.* analysed 46 randomised controlled trials which evaluated 13 types of comfort interventions grouped into four categories: audio-visual, physical, psychological, and "others" (education/information, aromatherapy). Most aromatherapy interventions, one audio-visual and one educational intervention, improved patient comfort based on anxiety levels and were considered clinically significant (20).

A notable presentation at ESTRO underscored the imperative of prioritising patient comfort within radiation therapy and delineated several strategies to alleviate anxiety, minimise discomfort, and enhance the overall patient experience. In his presentation titled "Role of music and ambient light and their impact on patients' immobilisation and verification," Philipp Scherer highlighted that despite comprehensive patient education, a subset of patients still experience anxiety and discomfort after the commencement of radiotherapy. The study involved 190 patients and revealed that dimmed light treatment rooms and relaxing music positively affected patient relaxation.

Changes in anxiety levels due to the colour of the treatment room were not reported to be significant, and there was no interference between the coloured light and surface guidance systems or between the background music and intrafraction movement or communication through the intercom system (21).

Given their regular interaction with patients during RT sessions, RTTs possess a unique vantage point to assess and address patients' needs and concerns. Beyond their technical responsibilities in treatment planning and delivery, RTTs offer patients crucial information and reassurance regarding treatment expectations and potential side effects. While assessing the breast cancer patients' perspectives, one study concluded that forming a good relationship with the RTTs and gaining information about their treatment increased their emotional comfort during RT (22). Mattarozzi *et al*. observed a noteworthy connection between patient satisfaction with the rapport established with RTTs and patients' perception of the intensity of pain induced by radiation therapy, as well as their overall attitudes toward the treatment process. The patients who perceived their interaction with RTTs as positive reported reduced pain intensity and had a more favourable disposition toward the entire RT experience (23). After analysing twelve papers in a systematic review by O'Neil et al., a similar conclusion was stated. The need for sufficient time spent with RTTs and the preference for continuity of RTTs during treatment positively influenced patients' perspectives (24).

An interesting qualitative study brought together both the patients' and the RTTs' points of view on comfort during RT. Both categories mentioned emotional health-related issues like stress, vulnerability and privacy and positioning/immobilisation-related experience. Information and communication were mentioned by patients only, as well as environmental experience determined by the first impression of treatment rooms (25).

Recognising the role of the holistic approach underlines the need for RTTs supplementary training, which could enhance communication and interpersonal proficiencies, a deeper understanding of patient psychology, and an increased emphasis on emotional intelligence. European Society for Radiotherapy and Oncology's core curriculum for RTTs includes the required knowledge and skills for advanced delineation and volume determination, treatment planning, imaging, quality and risk management, brachytherapy, management and service development, patient care and support, and research (18).

3. Conclusion

Recent technological improvements in the RT field, like IGRT, ART, SGRT and AI-based solutions, are bringing the opportunity for RTTs to grow and develop their role in the multidisciplinary team. Educational interventions empower the RTTs to improve their skills, deliver quality treatment, efficiently educate patients and contribute to RT research.

Abbreviations:
RTT – radiation therapy technologist
RT – radiation therapy
IGRT – image-guided radiotherapy
ART – adaptive radiotherapy
SGRT- surface-guided radiotherapy
AI – artificial intelligence
ESTRO - European Society for Therapeutic Radiology and Oncology
CT – computed tomography
MRI – magnetic resonance imaging

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Author's contributions: EMV, NKV and MEC selected the material, EMV and MEC wrote the text. JvdB reviewed and improved the manuscript.

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In Pursuit of Meaningfulness in the Biomedical Literature – Notes from a Scrap Booklet

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About our guest

Professor Søren M. Bentzen is the Director of the Division of Biostatistics and Bioinformatics, Department of Epidemiology and Public Health, University of Maryland School of Medicine, USA, and he is also an Adjunct Professor of Radiobiology and Medical Physics, University of Copenhagen, Denmark.

Dr. Bentzen received a Master of Sciences in physics and mathematics, a PhD in medical image analysis, and he is a doctor of medical science in quantitative clinical radiobiology. He was one of the leaders of the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) initiative, and serves as a member of the Pediatric Normal Tissue Effects in the Clinic (PENTEC) steering committee. He was also a member of the American Society for Radiation Oncology (ASTRO) Task Forces to develop evidence-based guidelines on the appropriate fractionation for whole breast irradiation and for localized prostate cancer. He has served as chair or member of 17 (seven currently active) Independent Data and Safety Monitoring Committees or Trial Steering Committees and as co-chair for Translational Research for two Radiation Therapy Oncology Group (RTOG) phase III trials.

He has published more than 500 original papers and book chapters, has presented >370 invited lectures, and he currently serves on 10 international cancer journal editorial boards. His main research interests include bioeffect modeling; biomathematics; applied biostatistics; clinical trial design; evidence-based medicine; late effects of radiotherapy; clinical radiobiology; integration of data from genomics, proteomics, and molecular imaging into novel therapeutic

Interviews

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strategies. He received more than 30 awards and honors by now, including the ASTRO Gold Medal and European Society for Radiation Oncology (ESTRO) Breuer Gold Medal (1).

This interview is meant to present in an interactive form some general elements that could help young clinicians to develop a critical approach when reading a medical research manuscript.

Keywords: *interview, radiation oncology, clinical trials, statistics, critical thinking, medical literature*

MC: Dear Professor Bentzen, you are, among many other roles, the Course Director of the ESTRO teaching course on Quantitative Methods in Radiation Oncology: Models, Trials and Clinical Outcomes. One of the topics presented during the course was "Critical Appraisal". I believe the ideas and concepts you mentioned during the lecture would be useful for young clinicians and researchers. What would be in your view the first rule for critically assessing a paper?

SMB: Read the paper – the whole paper. Sometimes, totally different statements are found in the title, in the abstract or in the body of the paper, on the same topic. We are overwhelmed by the quantity of published papers. In 2020, there were more than 30 million records in Pubmed, with 800 000 new records added each year. The abstract is the part of the paper which has the biggest chance of being read. An interesting analysis was done by Pitkin *et al*, assessing random samples of 44 articles published during one year in each of five major medical journals at that time: *Annals of Internal Medicine*, *British Medical Journal*, *Journal of American Medical Association, Lancet* and *New England Journal of Medicine*, and 44 consecutive papers in the *Canadian Medical Association Journal*. Abstracts were considered deficient if they contained data that were inconsistent with data in the article or not found in the body of the paper at all. The proportion of the deficient abstracts varied from 18% to 68% (2). It is not evident whether the situation has improved since then; so, read the whole paper not just the abstract.

MC: This makes citation based on abstracts a risky bet, isn't it? What do you think about citing a paper based on its citation in another paper?

SMB: Never use secondary citations. This is another trap. Just an example to illustrate this is a paper by Evans *et al*, in which they evaluated fifty randomly selected references from a single months' issue of three journals: the *American Journal of Surgery*; *Surgery, Gynecology and Obstetrics*; and *Surgery.* A major error of citation was assigned if the referenced article failed to substantiate, was unrelated to or even contradicted the assertion made by the quoting authors. Of the fifty randomly selected citations, thirteen major and 41 minor citation errors were found (3).

MC: We agree that we have to read the paper, but how to read it? What should we take into account?

SMB: It would be impossible to give a miraculous recipe or to cover all the details in a limited amount of text. A simple checklist could look like this:

- **Design – Is it appropriate for the question?**
- **Patients – Are they representative? Is there a selection bias?**
- **Interventions – Are they well defined and feasible? What was the compliance?**
- **Outcome measures (endpoints) – Are they relevant and clearly defined? Are any missing? Many oncology papers do not give quantitative data on adverse events (4).**
- **Results – How are they analyzed and presented?**

MC: Speaking about patients included in clinical trials, I remember discussions regarding the comparison of patients from the real world and patients from clinical trials. What is your opinion on this topic?

SMB: The cohorts would need both **internal and external validity**. The internal validity represents the extent to which the observed difference between groups can be correctly attributed to the intervention and it is threatened by bias and sampling variability. This is why we give the highest weight to data from

randomized controlled trials. The external validity is the extent to which study findings can be generalized to a population. Trial populations are often selected in order to limit the variability among cases within the trial – but this may make the trial population less representative of unselected cases seen in the clinic.

Another important element to evaluate is the **Intention-to-treat principle**. Are the patients analyzed as members of the treatment group to which they were randomized, regardless of actual treatment? Randomization only controls bias at the time of randomization. This should be the primary analysis of the outcome of any trial.

MC: I understand that the more changes are made to the initial plan, the more errors and bias can occur. Sometimes we read about results from sub-group analysis. What are your thoughts about their relevance?

SMB: That depends if the sub-group analysis was planned from the beginning or not. The primary clinical endpoint would have to be selected before the trial starts and investigators should be blinded to accumulating data. **We make our bet before the race begins**.

A retrospective cohort study on data from protocols and publications of 62 clinical trials showed that information on sample size calculations and statistical methods were often not specified or had unacknowledged discrepancies between what was in the protocol and what was included in the publication of the results (5).

MC: It seems that it would be necessary that a clinician have solid statistics knowledge, in order to spot the flaws. What do you think?

SMB: I don't think you need a degree in statistics to read a paper in a medical journal. However, there are multiple statistical methods used in medical papers and having at least a basic understanding of these would be useful. Also, there are a number of pitfalls in the analysis and interpretation of clinical data and it is extremely helpful also for biologists and clinicians to be aware of many of these. An example is the analysis of Marsh and Hawkins, dating from almost three decades ago, when they analyzed 44 reports on multicenter randomized controlled trials (RCTs). If someone would have wanted to understand at least half of them, it would have had to be familiar with 11 statistics techniques, including t-tests, power estimation, life tables, survival statistics, the Cox regression model and analysis of variance (6). Anyway, since then a variety of statistical methods became even more widely used in medical research, in part as a result of the availability of inexpensive statistical software packages. However, you still need input from biostatisticians in the context of the increasing amount of available data. According to the US Bureau of Labor Statistics, data scientists and statisticians are among the top 10 fastest growing occupations estimated for 2021-2031 (7).

MC: That's good news for the clinicians and researchers – when starting a clinical trial we will have a better chance to design it well if we will have a statistician within the team.

SMB: Sir Ronald A. Fisher - a British mathematician, statistician, biologist and geneticist, considered as one of the founders of modern statistical science – stated that: "To call in the statistician after the experiment is done may be no more than asking him to perform a postmortem examination – he may be able to say what the experiment died of." Talk to a statistician, already from the design stage,

MC: Continuing the parallel from this inspiring quote, what are the "signs and symptoms" that we would have to assess when examining a "body of evidence"?

SMB: It would depend on the degree of complexity of the "case". We can mention some simple aspects that should not be missed.

Ideally, a RCT should be designed to answer a specific question. Two types of errors can occur – concluding that the hypothesis is false, when it is not, or the opposite. The size of the trial strongly influences its power and the statistical significance of an observed effect. However, this also means that the *P* value itself can give a false impression of the importance of trial findings. C**onfidence intervals around the estimated effect size** are so much more informative that just the *P* value (8).

However, there are observational, or registry studies in which a large amount of data is available. Here, we can fall into another trap. When the sample size is large enough, a very small difference becomes

statistically significant. Large databases like the US National Cancer Data Base (NCDB), which includes patient and treatment data from more than 1500 cancer programs and more than 34 million unique cases, is such an example of a "tall data" source. In the "tall data", the number of cases is high and the number of tested features is low. A proof of concept was done testing the hypothesis that the incidence of nodal metastasis as a biomarker in two samples of one million women. The *P* was < 0.05 and the confidence interval was ± 0.3%, for a real difference of 0.15% (9). We should always apply the clinical judgment and sound critical sense when reading results. Numbers are important, but **a difference is only a difference… if it makes a difference.**

MC: The same facts can be presented in a more or less "appealing" way, which would lead to a different impact on the viewer.

SMB: Exactly. Another thing that we should pay attention to is to the way the data are presented. Relative risk estimates are often more impressive than absolute risk estimates. A questionnaire presented to respondents gave the same results in two different ways: as an absolute change in outcome rates (overall mortality reduction from 7.8% to 6.3% meaning a difference of 1.5%) or a relative reduction (of 20.3%). Both differences were stated as statistically significant, but almost half of the respondents perceived them as different and almost 90% of those were inclined to change their clinical practice based on the relative change in the outcome rate (10).

MC: Are there other factors that would lead to the overestimation of the importance of a certain treatment, except for our personal interpretation of data?

SMB: We can think of publication bias. There is a higher tendency of reporting statistically significant effects and there might be also a delay in publishing negative results. There is also the risk of duplicate publication of data from trials demonstrating larger treatment effects. A classic example is ondasetron. A metaanalysis including duplicated data overestimated the efficacy of ondasetron by 23%

MC: What about studies that show a strong correlation between two variables?

SMB: Correlation does not necessary imply causality. Some statistical results would support hilarious conclusions, if we would take correlations as causality. There is a significant correlation between stork populations and human birth rates across Europe (P=0.008) (11) and between the divorce rate and margarine consumption in Maine, USA (correlation 0.9925, P<0.0001) (12). Clearly, these are not meaningful findings.

MC: How should we read and understand a positive trial? Could it have a false positive conclusion?

SMB: There could be sources of errors in positive trials. Multiple comparisons due to multiple endpoints, repeated looks and subgroup analysis could impair the chances of a correct result in the absence of adequate statistics. Bias coming from post-randomization exclusion or other causes should be avoided. Even if the trial is randomized, there could still be biases introduced by, say, differences in diagnostic intensity or in supportive care, that cannot simply be attributed to the treatment itself.

MC: What about negative trials?

SMB: Absence of proof is not proof of absence. Except for the sample size, there are other factors that would lead to a type II error – failing to detect a real difference between two interventions. We can mention heterogeneity (in patient populations, diagnostic, quality of care and follow-up procedures), short follow-up or high rate of loss of patients from follow-up.

MC: Is it mandatory to have a randomized controlled trial to support the implementation of a new treatment or technique?

SMB: Randomized controlled phase III trials are the gold standard for assessing differential benefits of two therapies. However, not all the current clinical practice is based on results of such trials. Leaving aside the anecdotic lack of evidence of the benefit of the use of parachutes (13) when jumping out of airplanes, there is no evidence from RCTs demonstrating the clinical benefit of simulators, CT-based

treatment planning, mega-voltage radiotherapy or other elements from our daily practice. However, if the aim is to show a better outcome from a technological innovation the need for randomized controlled trials remains. We are used to this in the case of a novel medication meant to improve outcome. This is equally valid for technology, but the immediate goal of a technical innovation is often to improve treatment quality, which may be demonstrable without randomization. We may fell that improved quality will impact the outcomes. But since survival outcomes are influenced by multiple factors, using them as indicators of treatment quality may have a low sensitivity and specificity. When deciding if a RCT is really needed and ethical, we should take into account the principle of equipoise, a balance of benefits and risks in both arms of the study. There are situations when we have reasons to believe that treatments would not be equivalents in terms of safety, so it would be unethical to enroll patients. Non-randomized or "observational" studies should be seen as a complement to RCTs (14).

MC: Do we still need to critically read a paper which has already gone through peer-review?

SMB: Peer review is a quality stamp, and not a warranty. We could give an example: Godlee *et al* introduced 8 deliberate errors or weaknesses in a manuscript ready for publication in British Medical Journal and sent it out for review. More than 200 potential reviewers responded, but the median number of spotted errors was 2, nobody commented on more than 5, and 1 in 6 reviewers did not comment on a single one. The rate of error detection was not modified by asking them to sign the reports or blinding them to the authors and origin of the paper (15).

MC: How can study quality or strength of evidence be objectively assessed?

SMB: The simple answer is: it cannot! There are multiple quality instruments and guidelines. Twenty years ago there were already 20 systems for evaluation of systematic reviews, 49 for RCTs and 40 for grading the strength of a body of evidence. Quality scores can be applied when evaluating the results of a trial. But although many of these instruments make some sense, there is not a single silver bullet that works across the whole range of trials. As Andrew S. Tannenbaum, an American-Dutch computer scientist, said: **The nice thing about standards is that there are so many of them to choose from.**

Abbreviations:
QUANTEC - Quantitative Analyses of Normal Tissue Effects in the Clinic
ASTRO - American Society for Radiation Oncology
RTOG - Radiation Therapy Oncology Group
ESTRO - European Society for Radiation Oncology
RCT - randomized controlled trial

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Art for Advanced Radiation Oncology – Synchronizing the Past and the Future for a Better Patient Care

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About our guest

Professor Maria Antonietta Gambacorta is a specialist in Radiation Oncology with a PhD in Brachytherapy. She is responsible for the Radiotherapy Oncology hospitalizations and the Interventional Oncology Center and the coordinator of the Multidisciplinary Group for the treatment of rectal tumors within the Comprehensive Cancer Centre of the Fondazione Policlinico Agostino Gemelli, Rome. Due to her level of expertise, she was elected member of the Board of Directors of the Italian Association of Radiation Oncology (AIRO); and member of the board for the drafting of the Guidelines on rectal cancer of the Italian Association of Medical Oncology.

Professor Gambacorta is a member of European Society of Radiation Oncology (ESTRO) where she carries out teaching activities in international courses of the ESTRO school. She has published more than 170 scientific publications in peer-reviewed journals, including the International consensus guidelines for Clinical Target Volume delineation in rectal cancer. In this interview, Professor Gambacorta shares some insights about the Art for ART project, implemented in the Radiotherapy department of Policinico Agostino Gemelli, Rome.

Keywords: *interview, radiation oncology, art, technology, quality of life*

Interviews

MC: What is, in your perspective, the connection between Medicine and Art?

MAG: Body and soul are inescapably united in the human being. We cannot just treat the body, we must also treat and support the soul. Medicine heals the body; art heals the soul. Both are means, the

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most powerful means we know, to heal the whole person; God (or fate) does the rest. Art is beauty, art is both objective and subjective, because it allows us to interpret it and to see what we want and need. Similar to medicine, don't you think?

MC: Indeed, if we look in the past, at the dawn of medicine, we can find that the ancient Greeks had the same God for both healing and art – Apollo. But coming back in the present days, we would like to know when, why and how did you and your team start to include art in patient care?

MAG: This project was born in 2012 from the idea of Professor Valentini, who is not only a talented radiation oncologist but also an art lover, and who wanted to combine his two passions. That was when we renovated our radiotherapy department. In our minds, it was just a way of improving the radiotherapy bunkers. But even then, we and I understood that the project he had in mind was more than that: 'healing with art'. What a utopian thought...

MC: What were the projects that followed?

MAG: The project that followed was bigger than expected. We now have several projects under the umbrella of 'art for ART' (the capital ART stands for Advanced Radiation Therapy).

We have a jukebox for radiotherapy sessions, where patients can use an app to choose the music they want to listen to during their treatment. We have a project for children who become the protagonists of stories during treatment and can also produce videos of their 'radiotherapy experience' to share with other young children and their families. We have a platform rich in artistic content (poems, books, paintings, museums, music...) covering different emotions (joy, love, compassion, nature...) (1).

MC: What were the patients' perception and feedback? What about the medical staff, too?

MAG: The patient needs to be involved and supported in the project.

There may be barriers to overcome, especially at the beginning. People have cancer, they want to be cured, they don't have the time or the desire to get involved in these "useless things". However, once they are in, after a few days, as they become familiar with the environment, the organisation and their new "tasks", they begin to open up to being involved in the project, and once they are in, they feel relieved and appreciate the system.

The medical staff and all the staff, although never relieved (I smile), receive back from the patients their gratitude. It is increasingly common to hear "I felt at home". This is the most rewarding feedback for us. These messages from patients are also shared among us and through our social networks in a column called "Seeds of Gratitude". “Seeds” because gratitude breeds wellbeing and wellbeing also eases the burden on healthcare workers (2).

MC: How did you measure the impact of these interventions?

MAG: That was the question I was expecting! The platform has an artificial intelligence system underneath that profiles the patient, suggests art content for sharing and links patients' choices with data on therapy continuity, lab tests, tumour responses.

We would like to show the impact of art therapy on cancer patients with numbers.

We already have a small publication on brain tumour patients showing that those who are more resilient and spiritual live longer. Is this a coincidence? I don't think so.

MC: What was the impact of those projects on the department' workflow and expenses?

MAG: The workflow is definitely improved, patients have time to devote to all stages of treatment: during chemotherapy they can devote to music videos, documentaries, during radiotherapy they can listen to their favourite music, the platform's content can also be used in waiting rooms. All of this content fills the time patients spend in their "new home", reducing the negative perceptions associated with their new condition in a broader sense.

The increased resilience of patients and the beauty of the workplace also bring relief to the souls of healthcare workers.

The costs of maintaining the system are all covered by donations. If I were to use a metaphor, I would describe it as a wheel that turns endlessly: donors donate, people continue their efforts to keep the project alive, patients and health workers benefit, and so on.

MC: How did you manage the inherent challenges that come with such changes?

MAG: How did I deal with the challenges? I can't say, at the moment I'm mostly benefiting from the changes!

MC: For those interested to learn more from your experience in this field, what would you recommend them to read?

MAG: First of all, the scientific literature that deals with these aspects, videos and internet content, our website gemelliart.it, the feedback from patients in the "seeds of gratitude" section on the @gemelliart facebook and instagram accounts. And then... just come and see!

MC: What about those who would like to implement a similar project? What should they start with, as first steps?

MAG: In Italy there is already experience in art and in general patient support, not only in radiotherapy but in medicine in general. We have a "rete.ART" with 4 hospitals following the same strand, but there are many Italian Radiotherapy Oncology that have independently sensitized themselves to this theme. European radiotherapy has started a process of humanizing treatment environments. In short, there is a lot going on.

The first step? Feel it inside!

MC: Are there future plans for continuing this project at Gemelli, or starting another one involving art, in any form?

MAG: Art is one of the expressions of beauty, and we have had the strength and opportunity to build a platform to link these difficult-to-measure aspects to clinical outcomes.

The results that we will get will certainly enable future developments. The platform can be expanded and anything that enhances well-being can be taken on board.

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