Low Radiation Doses in Oncocytic Lesions of the Parotid Gland: A Double-edged Sword. A Comprehensive Review

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Oncocytic lesions represent a group of benign and potentially precancerous tumors characterized by the accumulation of oncocytes, which are large, granular, and eosinophilic cells. Diagnosing oncocytic lesions in the parotid gland typically involves a combination of imaging techniques, such as ultrasound, Computed Tomography (CT) scans, and Magnetic Resonance Imaging (MRI). Fine-needle aspiration (FNA) biopsy with histopathological examination remains the primary diagnostic tool for these lesions. Accurate diagnosis is crucial for appropriate management decisions.

Treatment options for oncocytic lesions in the parotid gland include surgery, conservative management, and radiation therapy (RT). However, in the head and neck region, radiation doses can be a double-edged sword. While RT is a treatment modality, low radiation doses can promote the development of oncocytic lesions in the parotid gland. The prognosis for patients with oncocytic lesions is generally favorable, especially when the lesions are benign and appropriately managed.

Current research focuses on the molecular mechanisms underlying oncocytic lesions in response to low-dose radiation exposure. The development of these lesions following low radiation doses represents a significant clinical concern. This manuscript provides a comprehensive overview of the current knowledge regarding oncocytic lesions in the parotid gland, including risk factors, diagnosis, treatment options, and ongoing research, offering valuable insights for clinicians and researchers.

Keywords: parotid gland; oncocytic cells; low radiation dose; oncocytoma; ionizing radiation; non-target effect; mitochondria

Introduction

The term "oncocyte" was introduced for the first time by Hamperl in 1931 [1] and the first case of oncocytoma was described in 1932 by Jaffe [2]. Oncocytic cells are characterized by eosinophilic granular cytoplasm with an accumulation of mitochondria, possibly due to mutations in mitochondrial DNA. The 4th edition of the World Health Organization (WHO) [3] classification defines oncocytic lesions of the salivary gland as nodular oncocytic hyperplasia (oncocytosis), oncocytoma, and oncocytic carcinoma. Nodular oncocytic hyperplasia, more commonly known as oncocytosis, is a nonneoplastic epithelial lesion. An intact capsule surrounds the oncocytoma and is histologically composed of sheets of epithelial cells with a central scar and abundant eosinophilic granular cytoplasm. Oncocytic carcinoma is characterized by a slow-growing mass with a locally infiltrative nature (capsular, vascular, or neural invasion) and a tendency to metastasize locally and distantly [4].

The parotid gland is involved in 78%–84% of cases, with bilateralism observed in 7% [5, 6]. They can also arise in the sinonasal region, larynx, lung, kidney, adrenal gland, thyroid, and pituitary gland [7, 8, 9, 10]. The Ki-67 immunostaining index and the expression of c-kit and Tumor Protein 53 (p53) have been suggested to differentiate oncocytic carcinoma from benign oncocytoma of the salivary glands. Additionally, Cluster Differentiation (CD) 10 and cytokeratin 20 have been used to distinguish between salivary gland oncocytomas and renal oncocytomas [11, 12]. Furthermore, oncocytoma may be considered an evolution of sialoadenosis due to a metaplastic-hyperplastic process [13].

Risk factors for oncocytic lesions include a history of radiation exposure five or more years prior to presentation and possible viral infection such as Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), human herpes virus-8 (HHV-8), human T-lymphotropic virus type 1

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(HTLV-1), and human papillomavirus (HPV) [14, 15]. The prognosis for patients with oncocytic lesions in the parotid gland is generally favorable, especially when the lesions are benign and appropriately managed [16].

Oncocytic lesions present a crucial and emerging area of concern in radiology and oncology. In an era marked by increasingly prevalent medical imaging and radiation-based treatments, understanding the impact of even low radiation doses on human tissues and organs is of paramount significance. The parotid gland, with its intricate architecture and critical role in saliva production, has garnered attention due to the potential development of oncocytic lesions following low-dose radiation exposure.

Previous studies have reported that low radiation doses can reprogram the tumor microenvironment. Specifically, radiation doses ranging from 0.5 to 2 Gray (Gy) promote the polarization of pro-tumor M2 macrophages to the antitumor M1 phenotype, normalize tumor blood vessels, increase infiltration of CD4+ T cells and Natural Killer (NK) cells, and downregulate the inhibitory cytokine Transforming Growth Factor-β (TGF-β) [17, 18]. This comprehensive review focuses on the complex relationship between low radiation dose exposure and the development of oncocytic lesions in the parotid gland, offering a detailed exploration of the underlying mechanisms and providing valuable insights into medical practice and patient care.

A comprehensive search was conducted on PubMed, MEDLINE, and the Cochrane database, covering literature from 1970–2024. This review analyzed preclinical cell studies, case reports, case series, randomized controlled trials, non-randomized controlled trials, and cohort studies to provide an extensive overview of current knowledge on oncocytic lesions, including risk factors, diagnosis, treatment options and ongoing research.

Materials and Methods: Literature Review

Study Selection

This literature review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [19] (Fig. 1). The goal was to comprehensively explore current knowledge on oncocytic lesions in the parotid gland, focusing on their association with low radiation doses. The methodology involved systematically analyzing relevant scientific articles, research papers, and medical literature. PubMed, MEDLINE, and Cochrane were utilized to identify relevant articles published between 1970–2024. Preference was given to studies published after 2000, although some older references were included based on their significance. Specific keywords used in the search included “parotid gland”, “oncocytic cells”, “low radiation dose”, “oncocytoma”, “ionizing radiation”, “non-target effect”, and “mitochondria”.

Criteria for Inclusion and Exclusion

The research prioritized recent and high-impact studies, including randomized controlled trials, prospective studies, and case reports. Studies were published in peer-reviewed journals primarily focusing on oncocytic lesions in the parotid gland. Exclusion criteria encompassed papers not in English, those outside the scope of this review, and duplicates. A minimum of two authors (AS, ABo) reviewed each study for relevance and assigned ratings. The quality and reliability of each selected study were assessed (PC, AP) using established criteria, considering study design, sample size, and methodology. Priority was given to studies with clear methods, statistical rigor, and relevance to the research focus.

Review of the Trials

Data on risk factors, diagnostic methods, treatment options, and molecular mechanisms associated with oncocytic lesions were extracted. A total of 745 papers were screened, of which 511 papers were excluded for reasons including abstracts, letters, proceedings from scientific meetings, editorials, expert opinions, reviews without original data, studies lacking relevant data, repetitive data, non-English language papers, and animal studies. Eligibility was assessed for 234 articles, and 202 articles were excluded for lacking data on oncocytic lesions and radiation therapy in the salivary gland or non-target effects. Ultimately, 32 studies were included in the review.

Our study synthesized information from the selected studies to construct a cohesive narrative on oncocytic lesions in the parotid gland, emphasizing the role of low radiation doses. Key findings were analyzed, patterns were identified, and discrepancies or gaps in the existing literature were addressed. The literature assessment considered contributions from various medical specialties, including radiation oncology, radiology, pathology, and surgery, to ensure a comprehensive and interdisciplinary approach.

We aimed to provide a robust foundation for the manuscript, offering valuable insights for clinicians and researchers. Furthermore, the reliability and validity of the information presented in the subsequent sections were ensured, contributing to a comprehensive understanding of oncocytic lesions in the parotid gland.

Limitations of the Methodology

The availability of high-quality studies mainly addressing the relationship between low radiation doses and oncocytic lesions is relatively limited. Numerous studies focus on broader aspects of head and neck cancers without detailed insights into the specific impact of low radiation doses on parotid gland lesions. Additionally, the studies included in the literature review exhibit heterogeneity in design, sample size, and methodologies. This diversity poses challenges for drawing uniform conclusions, necessitating caution when generalizing findings across studies.

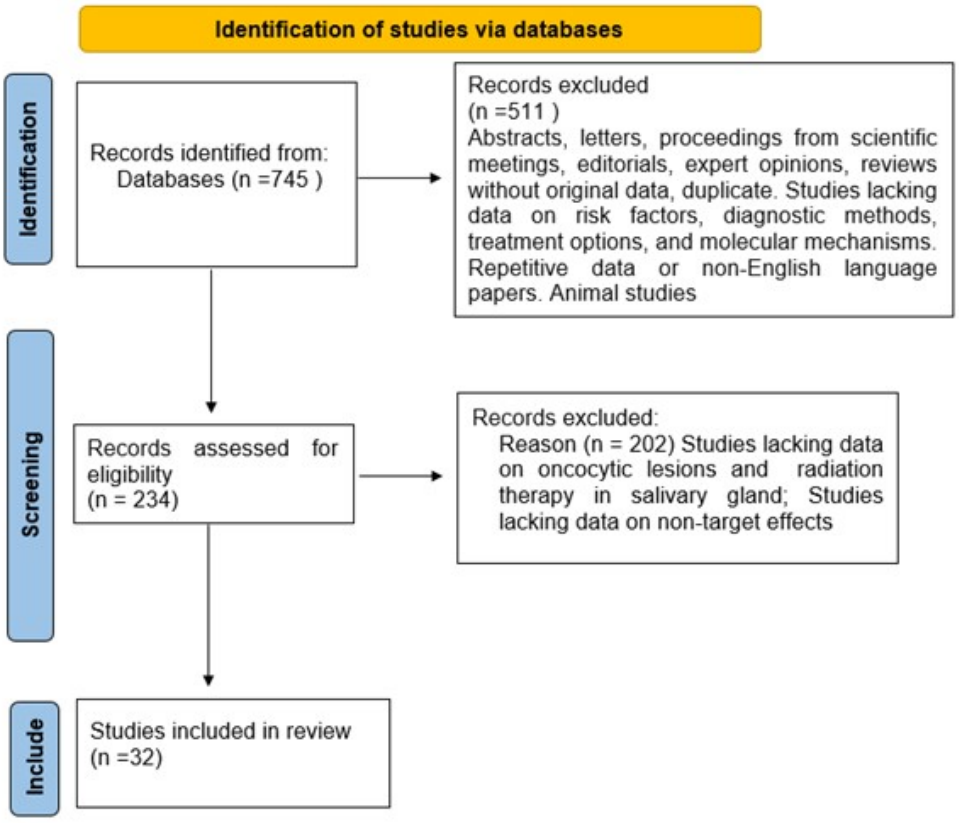

Fig. 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.

Publication bias is another concern, where positive results are more likely to be published, while studies with null or negative findings may be underrepresented. This bias could affect the overall interpretation of the literature. Furthermore, a significant number of studies are case reports, which may not provide robust evidence compared to randomized controlled trials or large cohort studies.

The field of oncocytic lesions and their relationship with low radiation doses are continuously evolving, leading us to include some dated references. Despite the advancements in research, the evidence base remains relatively small. The included studies may not fully represent the most recent advancements, and new research findings could influence the conclusions drawn in this manuscript. While efforts have been made to incorporate insights from various medical specialties, including radiation oncology, radiology, and surgery, there may be gaps in interdisciplinary coverage. Collaborative studies integrating perspectives from different specialties are limited. Moreover, the terminology and classification of oncocytic lesions vary across studies and medical literature. The lack of standardized terminology introduces ambiguity and challenges in comparing and synthesizing findings.

Diagnosis

Accurate and timely diagnosis of oncocytic lesions in the parotid gland is paramount for guiding appropriate management decisions. The diagnosis typically involves a multidisciplinary approach, encompassing clinical, imaging, and pathological assessments. The intricate nature of these lesions necessitates a comprehensive diagnostic strategy. Correlating information from different modalities enhances diagnostic accuracy and facilitates personalized treatment planning. The integration of advanced imaging techniques, minimally invasive biopsy procedures, and molecular markers contributes to the understanding of oncocytic lesions, tailoring interventions based on the specific characteristics of each case [11–27]

Clinical Characteristics

Clinical evaluation is crucial in the initial detection of these lesions. Physicians should thoroughly examine characteristics such as painless, slow-growing, lobulated, and mobile masses. Additional clinical manifestations, such as pain or facial nerve paralysis, may be present in some cases. These symptoms, combined with the medical history of the patient, contribute to the clinical suspicion of oncocytic lesions [11, 14].

Biopsy and Classification

Histopathological examination obtained via fine-needle aspiration (FNA) biopsy or surgical excision provides a definitive diagnosis, allowing differentiation between benign and potentially precancerous or malignant oncocytic lesions [20]. FNA contributes to the qualification process based on the Milan classification system, considering cellular features and molecular markers, which categorizes oncocytic lesions into three main groups: oncocytosis, oncocytoma, and oncocytic carcinoma, guiding appropriate treatment decisions [21].

The Ki-67 Labeling Index (LI) is a critical marker used to determine the proliferative activity of cells. A higher Ki-67 LI suggests increased cellular proliferation and is associated with more aggressive behavior in oncocytic lesions. It is an instrumental tool in distinguishing between benign oncocytomas and potentially malignant oncocytic carcinomas. In the Milan classification, the presence of frequent mitoses and cellular pleomorphism and a high Ki-67 LI support the diagnosis of oncocytic carcinoma. Immunostaining techniques, including Ki-67, c-kit, p53, CD10, and cytokeratin 20, may also be employed to aid in distinguishing oncocytic lesions [11, 12].

Imaging

Oncocytic lesions in the parotid gland are often found during follow-up imaging (Magnetic Resonance Imaging (MRI) and Computed Tomography (CT)) in patients undergoing radiotherapy treatments in the head and neck region. These lesions manifest as discrete, well-defined masses with varying degrees of enhancement on contrast-enhanced imaging [22]. Diagnostic imaging studies include ultrasound (US), CT, MRI, and positron emission tomography (PET), with Whartin's tumors considered in the differential diagnosis of oncocytoma [15].

Ultrasound (US)

US with Doppler evaluation is necessary to evaluate vessel density within the nodule parenchyma. US features show vessel branches extending from the periphery to the central area, similar to renal oncocytoma (Fig. 2) [23, 24, 25].

Computed Tomography (CT)

CT scans may reveal low-density areas within the parotid gland, often with mild to moderate contrast enhancement, allowing for a precise assessment of the density and distribution of the lesions [22].

Magnetic Resonance Imaging (MRI)

On MRI, these lesions often exhibit intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted images, distinguishing them from the surrounding normal tissue. Additionally, using contrast agents can enhance the vascularization within these lesions, aiding in their detection and characterization. MRI is particularly useful in distinguishing oncocytomas from oncocytic carcinoma [16].

Positron Emission Tomography (PET)

Oncocytic lesions present high F-18 fluorodeoxyglucose (18F-FDG) uptake due to their origin in the epithelium of the salivary duct and the accumulation of mitochondria in oncocytic cells (Fig. 3) [26, 27].

Multifactorial Diagnostic Process, Decision Support System (DSS), and Differential Diagnosis

Ongoing research focuses on the molecular mechanisms underlying oncocytic lesions in response to low-dose radiation exposure, providing insights into potential biomarkers for early diagnosis. The combined information from CT and MRI facilitates early lesion detection and offers critical insights into their size, location, and possible impact on parotid gland function, which are essential for guiding clinical decision-making and patient management in cases of low radiation-induced oncocytic lesions. CT and MRI are beneficial for assessing possible infiltration of bones or deep structures when US findings are unclear [23, 24, 25].

While imaging studies, including PET scans with high FDG uptake, may raise suspicion, frozen section examination enables real-time assessment of tissue during surgery, assisting in immediate decision-making. Definite malignancy criteria include the frequent mitoses, cellular pleomorphism, local invasion, capsular, perineural, intravascular, or lymphatic invasion, and regional or distant metastases [16]. The Milan classification emphasizes the importance of histopathological examination, and frozen section examination can be a valuable intraoperative tool.

Differential diagnosis with Warthin's tumor, another common parotid gland lesion with high FDG uptake, is essential. Oncocytic lesions and Warthin's tumor may exhibit increased FDG uptake, emphasizing the need for precise qualification [26, 27]. FNA, combined with histopathological analysis, plays a pivotal role in distinguishing between different entities.

A Decision Support System (DSS) plays a pivotal role in differentiating between imaging modalities for diagnosing oncocytic lesions in the parotid gland. The intricate nature

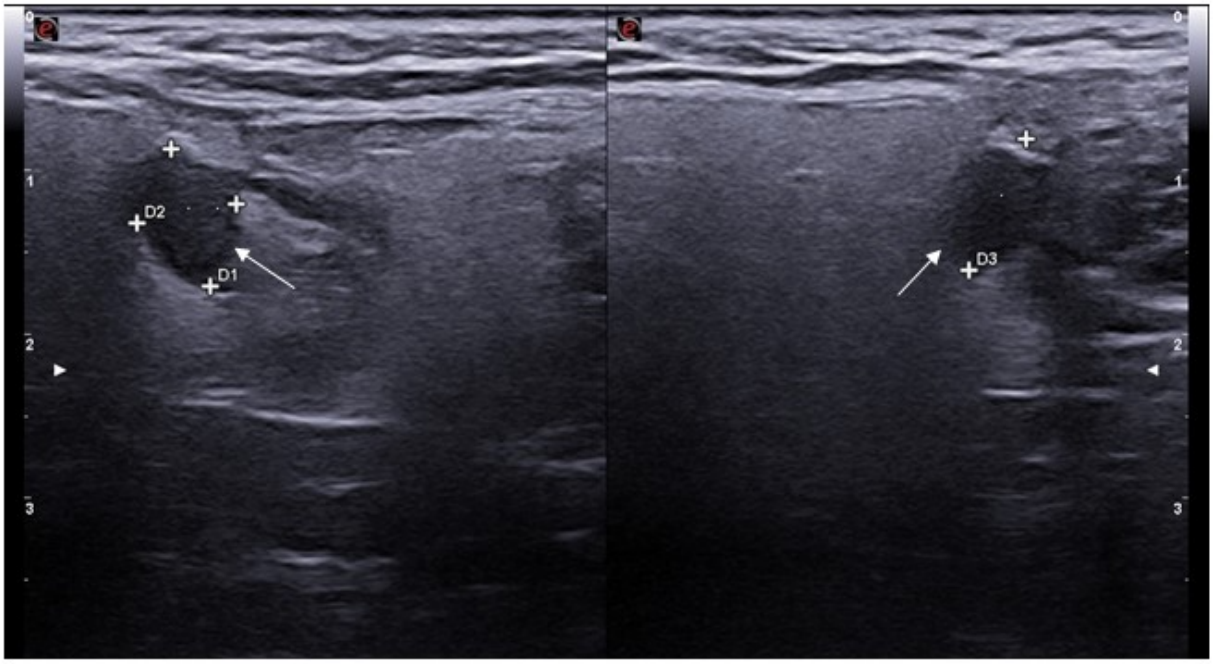

Fig. 2. Ultrasound images of oncocytic lesion in the parotid gland. The ultrasound examination shows, in the contest of the parotid gland, the presence of a hypoechoic formation with regular margin. Fine-needle aspiration (FNA) was performed and the results was an oncocytic lesion (white arrow). It presents a diameter of 8.7 mm × 6.2 mm × 8.7 mm. This image was collected from the internal hospital archive of A.O.U. "G. Martino", University of Messina and informed consent has been obtained from the patient.

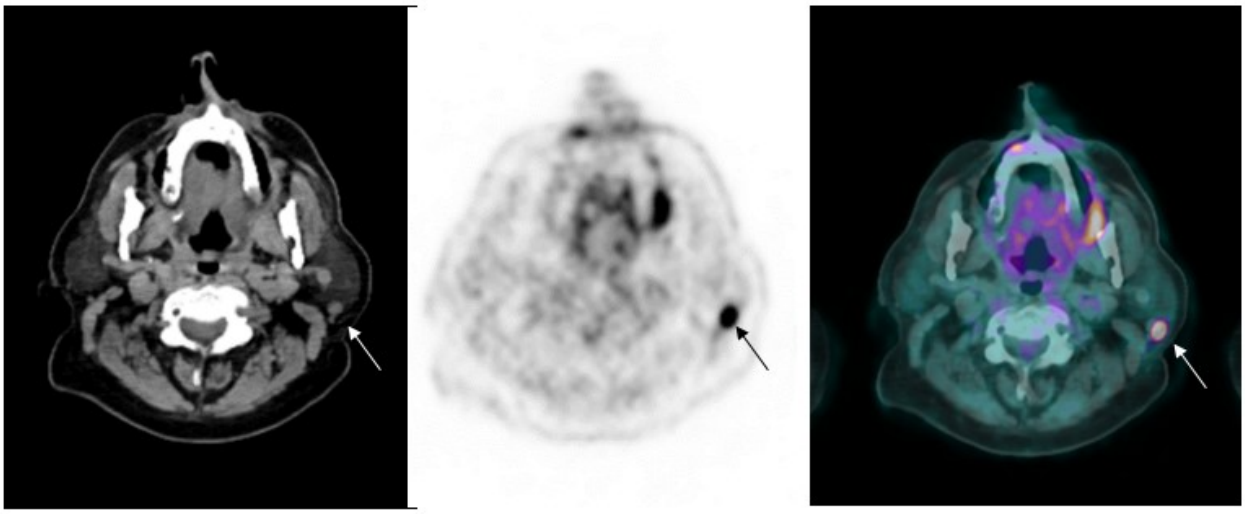

Fig. 3. Example of F-18 fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) uptake in the nodular area within the left parotid gland. The arrows show the nodular area within the left parotid gland in Computed Tomography (CT) scan and the respective high 18F-FDG uptake in PET scan. This image was collected from the internal hospital archive of A.O.U. "G. Martino", University of Messina and informed consent has been obtained from the patient.

of these lesions, their potential association with low radiation doses, and the diverse characteristics captured by various imaging modalities necessitate a sophisticated analytical approach. A DSS, utilizing advanced algorithms and machine learning techniques, can assist clinicians in interpreting and distinguishing imaging results from modalities

such as US, CT, and MRI [28]. By processing intricate patterns, densities, and vascularization revealed by each modality, a DSS provides valuable insights into the specific features indicative of oncocytic lesions. This aids in refining the diagnostic process, ensuring accurate identification, and contributing to personalized treatment planning. The integration of a DSS in the decision-making workflow enhances the efficiency and precision of differentiating image modalities, facilitating a more nuanced understanding of oncocytic lesions in the parotid gland [29].

Treatment Options

The treatment approach for oncocytic lesions in the parotid gland depends on the malignancy of the lesion. In cases of oncocytosis or oncocytoma, which are generally benign, a conservative "wait and see" policy may be considered, similar to the approach used for Warthin's tumor. This strategy involves regular monitoring through imaging studies to observe lesion behavior over time. For oncocytic carcinomas, a more aggressive stance is often necessary. Surgical intervention, such as parotidectomy, may be warranted depending on factors like lesion size, location, and clinical symptoms. The decision to perform neck dissection should be carefully considered, especially if there is evidence of regional lymph node involvement [11, 14, 27].

Surgery

Surgical intervention is pivotal in managing oncocytic lesions induced by low radiation doses in the parotid gland. The decision to pursue surgery is often based on factors such as lesion size, location, clinical symptoms, and the presence of suspicious characteristics that may suggest malignancy. Depending on the specifics of each case, various surgical approaches can be considered, ranging from a partial parotidectomy, which involves the removal of a portion of the gland while preserving its function, to total parotidectomy in cases where the lesion or surrounding structures necessitate a more extensive resection.

The surgical procedure aims to excise the lesion while preserving the integrity of the facial nerve, a critical concern due to its proximity to the parotid gland. Advancements in surgical techniques, including nerve monitoring and reconstruction, have contributed to improved outcomes in terms of both tumor control and postoperative facial function. Close collaboration between the surgical team and other specialists, including radiologists and pathologists, ensures accurate preoperative assessment, meticulous surgical planning, and comprehensive postoperative care.

Surgical treatment, when executed with precision and care, offers a promising avenue for managing oncocytic lesions in the parotid gland induced by low radiation doses to preserve oncological and functional outcomes. Given the rarity of these tumors, a standard management approach is lacking.

Numerous studies have reported case series of sinonasal oncocytomas and oncocytic carcinomas that underwent surgical resection with the endoscopic approach or lateral rhinotomy in cases of limited sinonasal involvement. In multiple recurrences and metastases, surgery, chemotherapy, and radiotherapy were performed [8, 30, 31, 32, 33, 34, 35, 36, 37]. Compared to the major salivary glands, oncocytic tumors of the sinonasal tract are more likely to be malignant, with more frequent local invasion and recurrence.

In the case of oncocytoma of the parotid glands, surgical resection with facial nerve preservation represents the optimal treatment to obtain a precise diagnosis and to reduce the recurrence rate, which is as high as 20–30% when a partial excision is performed [38].

Radiotherapy

Radiotherapy is emerging as a valuable treatment modality, primarily in cases where surgical intervention is not the primary choice or poses significant risks to the quality of life of the patient. Ionizing radiation can effectively target and shrink oncocytic lesions, disrupting their growth and reducing associated symptoms.

Postoperative radiation therapy is the primary treatment for head and neck cancer patients and represents a useful therapeutic approach in oncocytic carcinoma with local invasion and destruction, regional and distant metastasis, and lymph node involvement to prevent recurrence and spread [39]. Treatment planning and patient selection are pivotal considerations, and close collaboration between radiation oncologists, radiologists, and other specialists is essential to ensure the best possible outcomes while mitigating potential side effects.

Precise radiation techniques, such as intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT), allow for highly focused radiation delivery while sparing adjacent healthy tissues and minimizing collateral damage to the parotid gland and adjacent structures. However, radiotherapy in this context mainly involves a delicate balance between tumor control and the preservation of gland function, as the function of parotid gland in saliva production is critical for the quality of life of the patient.

Radiotherapy for low radiation dose-induced oncocytic lesions in the parotid gland presents a promising non-invasive therapeutic option, primarily when surgical intervention is associated with substantial risks or in cases of inoperable tumors. The role of radiation therapy in oncocytoma represents a double-edged sword because it is mainly related to onset rather than treatment. Previous issues reported that radiotherapy may induce volume changes and dysfunction in parotid glands, with significant damage when the radiation dose is greater than about 25 Gy [39, 40, 41].

Adverse Effects

Complications associated with the treatment of oncocytic lesions include those related to surgery, such as facial nerve

injury and postoperative infection [38]. Several studies have reported a decrease in the volume of parotid and submandibular glands during radiation therapy (RT) due to the direct effect of ionizing rays on the various glandular structures. Furthermore, the initial volumes and exposure to low radiation doses of the parotid glands correlate significantly with the grade of xerostomia [42, 43, 44].

The post-radiotherapy change in the volume and dysfunction of the parotid gland emphasizes the importance of weighing the benefits against potential adverse effects [43]. The prognosis for oncocytic lesions is generally favorable, especially in cases of benign oncocytomas that are appropriately managed. However, in oncocytic carcinoma, factors such as the extent of invasion and metastasis significantly influence prognosis [11].

The decision-making process for treatment and the assessment of prognosis should involve interdisciplinary collaboration among surgeons, radiation oncologists, and other specialists. Continuous monitoring and follow-up are crucial to evaluate treatment efficacy and address potential complications. Ongoing research will contribute to refining treatment strategies, optimizing outcomes, and enhancing our understanding of the long-term impact of various therapeutic interventions on patients with oncocytic lesions in the parotid gland.

Low Radiation Doses (LD) and Mitochondrial Effects

The impacts of low radiation doses (LD) on the parotid gland and the development of oncocytic lesions have recently garnered significant attention due to a growing body of research shedding light on the underlying mitochondrial effects. Mitochondria, the cellular powerhouses responsible for energy production, play a central role in cell function and health.

When exposed to low doses of radiation, it has been observed that mitochondria within parotid gland cells can undergo alterations, leading to the accumulation of oncocytic features. These changes may include mitochondrial enlargement, cristae remodeling, and increased numbers of mitochondria in affected cells. The intricate relationship between LD and mitochondrial effects in the context of oncocytic lesions in the parotid gland is a compelling area of investigation, and a better understanding of these mechanisms is crucial for advancing diagnostic and therapeutic approaches for managing this condition.

The effects of ionizing radiation can be divided into stochastic and deterministic effects. The probability that stochastic effects occur, but not their severity, is related to dose regardless of threshold. On the other hand, for deterministic effects, the likelihood and severity of an impact vary with dose and threshold [45].

Non-target effects such as hormesis, radio-adaptive effects, low-dose hypersensitivity, bystander effects (BE), and genomic instability are characterized by cellular responses that occur in cells where energy from ionizing radiation has not been deposited, implying that radiation affects other targets in addition to directly irradiated cells [46]. The different effects of radiation therapy depend on the delivered dose [17, 47, 48, 49, 50, 51]. It is known that low doses ($<$100 mGy) have proinflammatory effects [18] and can determine non-target effects (NTE) involving cellular signaling, particularly mitochondria-mediated signaling [52, 53, 54, 55]. Mitochondria support the immune system by providing the energy requirement and maintaining system activation by producing reactive oxygen species (ROS) and essential metabolites. Furthermore, LD induces mitochondrial pro-apoptotic events and elicits immunogenic responses. Maeda *et al*. [56] showed that irradiation of the cytoplasm could affect mitochondrial functions, particularly the mitochondrial production of ATP and antioxidant enzymes.

Maguire *et al*. [57] reported that doses $<$5 mGy increase mitochondrial mass. The effect of ionizing radiation and aging processing leads to nuclear DNA alteration and the replacement of chromosomal DNA with mitochondrial DNA. From the end of irradiation, the cytoplasm of epithelial cells becomes markedly eosinophilic, as seen in oncocytic cells. This process induces metaplastic transformation of the epithelial cells into oncocytes [58].

Discussion

To date, the exposure of parotid glands to low radiation doses has primarily been evaluated for the onset of xerostomia [40, 42, 43]. Our interest in clarifying the role of low radiation doses on the development of oncocytic lesions stems from our clinical observations. We encountered a patient with oncocytic lesions in parotid glands who had a history of radiation therapy for paranasal sinus carcinoma. Consequently, we retrospectively assessed the exposure of the parotid glands to low radiation doses.

Ionizing radiation has been identified as one of the risk factors in the development of oncocytic tumors. Brandwein and Huvos [59] reported a case series of 68 patients with oncocytic major salivary gland tumors, with follow-up available for 44 patients. Of these, 20%, with a median age of 43 years, had undergone previous radiotherapy, and in 5 cases, the radiotherapy field involved the parotid glands [59]. Exposure to irradiation through large roentgen doses or intense focal radiation from interstitial radon can lead to sclerotic changes in human submandibular salivary glands, which may mimic secondary lymph nodal tumors [60].

By 1977, Busuttil [61] reported the vascular and epithelial changes observed in the salivary glands after irradiation, attributing these changes to the direct effect of the ionizing radiation on various glandular structures. Autopsy samples of patients with head and neck cancers who underwent radiotherapy revealed nuclear pleomorphisms in parts of the gland within the irradiation field. Notably, the periphery of the irradiation zone showed fewer atrophic changes and a presence of oncocytic changes in the cytoplasm [61].

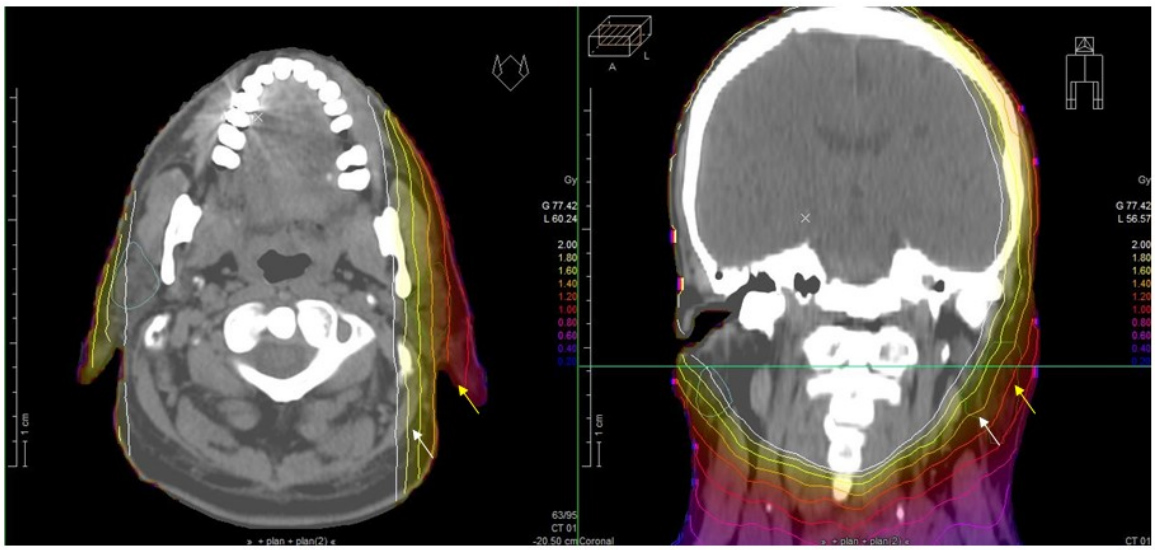

Fig. 4. Distribution of low doses related to radiation therapy treatment. The withe and yellow arrows show the isodose line corresponding to 1.8 Gy and 1.2 Gy respectively. Gy, Gray. This image was collected from the internal hospital archive of A.O.U. "G. Martino", University of Messina and informed consent has been obtained from the patient.

The delayed effects of ionizing on human cells are defined as non-target effects [61]. Among these, hormesis represents the stimulating phenomenon of low-dose radiation, characterized by a dose-response relationship where low doses stimulate, and high doses inhibit cellular responses [62]. Recently, Averbeck [46] focused on ionizing radiation-induced immune responses. Mitochondria are central to innate and adaptive immune defenses [63, 64]. Low doses of radiation can enhance mitochondria-dependent immune responses and the activation of Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) [65].

Mitohormesis is a biological process wherein low-level mitochondrial stress induces an adaptive response that enhances health and longevity [66]. This response activates cytosolic signaling pathways and releases ROS, mitochondrial metabolites, proteotoxic signals, and the mitochondria-cytosol stress response. Mitochondria-derived messengers and exosomes act as signaling molecules between cells, leading to genomic instability, mutations, and cell transformation while stimulating the immune system.

Mitochondrial DNA (mtDNA) has different repair mechanisms than cDNA and is more susceptible to radiation. Nugent and Liu demonstrated that doses ranging from 0.005 to 5.0 Gy increased mitochondrial mass, supporting the theory that mitochondrial fusion increases after irradiation [67, 68, 69].

In our case, as illustrated in Fig. 4, the oncocytic lesion developed 11 years after the patient received radiotherapy within the field covered by low doses (less than 1.8 Gy), supporting the theory that aging and ionizing radiation contribute to an increase in mitochondrial DNA.

Future Research

The complex interplay between oncocytic lesions in the parotid gland and low radiation doses presents a compelling area for future research, offering the potential to deepen our understanding, refine diagnostic approaches, and optimize therapeutic strategies. Several avenues warrant exploration to address existing gaps and propel the field forward.

Molecular mechanisms and biomarkers are key issues in future research. Investigating the molecular mechanisms underlying oncocytic lesions in response to low-dose radiation exposure is crucial. Future research should examine the specific pathways and genetic alterations contributing to these lesions. Identifying reliable biomarkers associated with oncocytic lesions could enhance early detection and prognosis assessment. A comprehensive understanding of the molecular landscape may unveil novel targets for diagnostic and therapeutic interventions.

Longitudinal studies examining the long-term effects of low radiation doses on the parotid gland are essential. This research should extend beyond the immediate development of oncocytic lesions to assess potential late-onset effects, including alterations in gland function and associated health outcomes.

Advancements in imaging techniques, such as refining the sensitivity and specificity of ultrasound, CT, and MRI, are pivotal for enhancing diagnostic accuracy. Future research should explore innovative imaging modalities and contrast agents to improve lesion detection, characterization, and delineation of adjacent structures.

Tailoring treatment strategies based on the specific characteristics of oncocytic lesions is an evolving area of inter-

est. Future research should focus on developing personalized treatment algorithms that consider the unique features of each lesion, patient factors, and the potential impact of prior radiation exposure.

Evaluating the impact of oncocytic lesions on the quality of life of affected individuals is crucial for comprehensive patient care. Future studies should explore patient-reported outcomes, addressing symptoms, functional impairment, and psychological well-being. Fostered collaboration among specialists from diverse fields, including radiation oncology, radiology, pathology, and surgery, is imperative. Future research should encourage interdisciplinary investigations that integrate expertise to provide holistic insights into oncocytic lesions and their management.

The role of potential risk factors, including radiation exposure and viral infections, merits further validation through large-scale studies. Identifying individuals at higher risk for developing oncocytic lesions can inform targeted screening and preventive strategies.

Collaborative efforts on an international scale can facilitate the pooling of data and resources, enabling the study of rare conditions such as oncocytic lesions. Multi-center studies and data-sharing initiatives can enhance the generalizability and robustness of research findings.

By prioritizing these research directions, the scientific community can advance our understanding of oncocytic lesions in the parotid gland, paving the way for improved diagnostic and therapeutic strategies. Integrating molecular insights, technological advancements, and patient-centered approaches holds the promise of transforming the management of oncocytic lesions and, ultimately, enhancing patient outcomes and quality of life.

Conclusions

Following low radiation doses, oncocytic lesions in the parotid gland represent a significant clinical concern. Further studies are essential to shed light on this multifaceted issue within radiation oncology and otolaryngology. The intricate relationship between low radiation doses and the development of oncocytic lesions in the parotid gland has emerged as a significant research topic with profound clinical implications. The evidence presented in this paper underscores the importance of recognizing the nuanced response of the parotid gland to even minimal radiation exposure and the potential impact on patient health. It is crucial to consider the molecular and cellular mechanisms involved and the associated clinical manifestations and diagnostic challenges.

Managing this pathology requires close collaboration among various medical specialties, including radiation oncologists, radiologists, pathologists, and surgeons, to facilitate accurate diagnosis, treatment planning, and effective interventions. As the medical community continues to refine its understanding of the impact of low radiation doses on the parotid gland, this research offers valuable insights that can inform clinical decision-making and improve patient outcomes.

The discussion of treatment modalities, such as surgery and radiotherapy, underscores the importance of tailoring therapeutic approaches to individual patient needs, considering the specific characteristics of the oncocytic lesions, the overall health of the patients, and their treatment preferences. The delicate balance between achieving tumor control and preserving gland function is a central theme in the management of oncocytic lesions, emphasizing the significance of patient-centered care.

Understanding the mitochondrial effects in this context elucidates the molecular basis underlying the development of oncocytic lesions, offering a promising avenue for further research and potential therapeutic targets. Addressing the intricate interplay between low radiation doses and mitochondrial changes can pave the way for future investigations and the development of novel interventions to prevent and treat these lesions.

In conclusion, ongoing studies and interdisciplinary collaboration are necessary to advance our understanding of this condition, refine diagnostic techniques, and optimize treatment strategies to improve the quality of life and long-term health outcomes for affected individuals. Despite the need for further research, existing literature suggests that low radiation doses may induce metaplastic transformation, leading to the onset of oncocytic lesions.

Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

Author Contributions

Conceptualization: AP, PC and SPe; methodology: AP, PC, ABo, AS; validation: AP, PC, MZ; formal analysis: AP and PC, ABr; design and interpretation of data: MZ, FFA; investigation: AP, PC, SPa; resources: AP, PC, MZ; data curation: AP, and PC, ABr; writing—original draft preparation: AP, PC, and FFA; writing—review and editing: AP, PC and SPe; visualization: AP, PC, SPa, SPe; supervision: AP, SPe; project administration: AP, PC, and MZ. All authors revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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