REVIEW ARTICLE

Clinical pathological features and radiotherapy treatment for adenoid cystic carcinoma of the head and neck: an update on recent evidence

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Keywords: Radiotherapy; Adenoid Cystic Carcinoma; Head and Neck Cancer;

ABSTRACT

Adenoid Cystic Carcinoma (ACC) is a slow-growing, locally invasive malignant tumour, with a deceptively benign histological appearance, a high probability of local recurrence and distant metastasis. The tumour comprises basaloid cells with small, angular and hyperchromatic nuclei and scarce cytoplasm arranged into three significant prognostic patterns: cribriform, tubular, and solid. In some tumours, dedifferentiation to a high-grade form occurs. The authors have reviewed numerous studies which have attempted to demonstrate accurate histological prognostic features, but these have often produced conflicting results.

The literature review suggests that Analysis of microarray and gene expression profiles provided new potential diagnostic and prognostic markers. However, tumor grade, lymph node metastasis, invasion of major nerves, and resection margin status continue to be the most consistent predictors of prognosis. The optimal treatment of ACC has not yet been fully established, although most studies advocate using surgical excision and postoperative radiotherapy. Careful tumor staging and grading with documentation of perineural invasion and margin status remain important prognostic tools. ACC has been incurable, and most patients will eventually succumb to local recurrence, distant metastasis, or both. The clinical course of the disease can be surprisingly heterogeneous, with some patients surviving decades and others surviving only months. The combination of surgery and radiotherapy in the postoperative period has shown the best locoregional disease control.

Contribution to Evidence-Based healthcare: This review contributes to a better understanding of the treatment of patients diagnosed with cystic adenocarcinoma of the head and neck, with regard to treatment with curative radiotherapy, as part of the proposed treatment or even to reduce the effects of the disease.

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What do we already know about this topic?
The optimal treatment for ACC has not yet been fully established. Careful staging and classification of the tumour with documentation of perineural invasion and margin status remain important prognostic tools. Once metastatic disease has occurred, especially in the lungs, many patients can survive for long periods. ACC has been incurable and most patients will eventually succumb to local recurrence, distant metastasis, or both.
What is the main contribution to Evidence-Based Practice from this article?
This study may contribute to the treatment of patients diagnosed with cystic adenocarcinoma of the head and neck, with regard to treatment with curative radiotherapy, as part of the proposed treatment or even to reduce the effects of the disease.
What are this research's implications towards health policy?
With this article, we can better target the treatment of ACC using RT.

Authors' Contributions Statement:
Gabriel Maluf: Designed the research methodology, performed data analysis, and contributed to the writing of the paper; Alberto Vianna: Acquired research data and contributed to the writing of the paper； Maria Graziela Kenupp: Organized data, participated in analysis; Uyeda Maria revised and submitted the manuscript; All authors read and approved the final version of the manuscript.

Introduction

Adenoid Cystic Carcinoma (ACC) is a malignant neoplasm with an unfavourable prognosis, despite its slow growth, because the tumour is capable of being aggressively invasive and having a high potential for recurrence (DeAngelis, Tsui, Wiesenfeld, & Chandu, 2011). Billroth first described this neoplasm in 1856 (Dantas, Morais, Macedo, Tinôco, & Morais, 2015).

ACC originates from ductal and myoepithelial cells along the intercalated ducts. It can develop in several anatomical sites, such as the major and minor salivary glands, lacrimal glands, and glands of the upper digestive tract (Bishop, Thompson, Wakely, Jr. Weinreb, 2021). In the maxillofacial region, it is responsible for approximately 22% of salivary gland neoplasms, with the minor salivary gland of the hard palate being the main site of involvement (Bovée, Inwards, Hogendoorn, Bloem, 2022). ACC is more prevalent in middle-aged adults and, according to several studies, regardless of sex (Belulescu et al., 2020). Distant metastases are common, with the lung being the most commonly affected site (Chang, Hsieh, Chen, & Chou, 2018). It may present clinically as a hardened nodule, with pain being an important finding. Ulcerated lesions that radiographically exhibit bone destruction can be visualized in the palate region (Dantas, Morais, Macedo, Tinôco, & Morais, 2015).

Histopathologically, ACC can be expressed as variable patterns, with three main types being recognized (Min et al., 2012). The Cribriform and tubular patterns, which present a lower aggressiveness and the solid pattern in which cellular pleomorphism and mitotic activity can be observed, as well as foci of necrosis in the centres of islands of neoplastic cells (Belulescu et al., 2020).

At present, surgery– usually followed by adjuvant radiotherapy (RT) - is the most effective treatment modality. Some reports have indicated that patients who undergo post-operative RT had an improved rate of survival compared with that of surgery alone (Cantù, 2021).

However, in unresectable cases or those with local recurrence after surgery, no efficient treatment strategy has yet been developed. Patients who undergo RT in the head and neck (HN) often develop changes and sequelae that are of interest in stomatology (Chang et al.,

2019).
The most common unfavourable side effects are xerostomia, mandibular osteoradionecrosis, mucositis, candidosis, dysphagia, trismus, and hearing loss.

Literature review
Gross pathology
The tumour is typically a firm, poorly circumscribed, nonencapsulated mass. The average size usually ranges from 1 to 8 cm in maximal dimension. Tumour size greater than 3 cm has been associated with increased rates of distant metastasis (Dai et al., 2020). The cut surface is white to greyish-white with a solid appearance. Haemorrhage and necrosis are rare features and should raise suspicion of high-grade transformation to dedifferentiated ACC (Jaso & Malhotra,2011).
Histopathology
The tumour has a heterogeneous microscopic appearance, consisting of varying amounts of 3 distinct growth patterns; however, the tumour cells have relatively uniform cytological characteristics. The tumour cells have a basaloid appearance, their angulated nuclei are hyperchromatic and their scant cytoplasm usually varies from being clear to eosinophilic. Electron microscopy and immunohistochemical analysis revealed that the tumour cells comprise two different cell populations that undergo either myoepithelial or intercalated duct cell differentiation (Fakhraei, Layegh, Darchini-Maragheh & Tayyebi Meybodi, 2022). Studies have described three growth patterns for ACC, where the cribriform pattern – the most frequent – is composed of islands of basaloid cells arranged in nests or islands surrounding cystic spaces of different sizes, forming a "Swiss cheese or sieve" pattern. The term "pseudocysts" is used for these cyst-like spaces, referring to the fact that they do not represent the true glandular lumen and are contiguous with the surrounding stroma (Jaso & Malhotra,2011). These pseudocysts can be identified as entities that "contain basophilic and/or eosinophilic glycosaminoglycans, periodic acid-Schiff-positive basal lamina material".
The tubular pattern cytology is similar to that of tumour cells, which are arranged in nests. These nests are surrounded by varying amounts of eosinophilic stroma that is often hyalinized. In addition, the stromal component was occasionally increased, thus compressing the tumour into fine strands that formed a trabecular pattern. In the tubular pattern, there are more prominent, well-formed ducts that have recognizable inner epithelial and outer myoepithelial layers when compared with the cribriform pattern (Jaso & Malhotra,2011).
The solid histologic subtype shows aggregates of basaloid cells without tubular or cystic formation. Although basaloid tumour cell cytology persists, larger tumour cells may be found and there may be more pronounced nuclear pleomorphism. As with the cribriform pattern, true ducts will sometimes be found between the cell layers (Jaso & Malhotra, 2011).
According to the Szanto system (Szanto, Luna, Tortoledo, White, 1984), "Grade I tumours contain only the tubular or cribriform growth pattern, grade II tumours contain cribriform or tubular growth with less than 30% solid component, and grade III tumours contain more than 30% solid component". The solid component is a consistent predictor of poor prognosis. Difficulty with classification arises because a tumour may show varying degrees of more than one histologic subtype. Several authors have reported that when using the American Joint Committee on Cancer (AJCC) tumour staging system, the results obtained were more predictive of prognosis and distant metastasis (Bradley, 2017).

The study cited above described high-grade or "dedifferentiated" ACC as an entity containing two histologic components: an area of conventional ACC of any grade and an area of high-grade undifferentiated carcinoma or poorly differentiated adenocarcinoma. The study reported that in a recent series, "the most common histologic appearance of the dedifferentiated component was slightly differentiated cribriform adenocarcinoma." Furthermore, it stated that the high-grade areas did not have histologic features of ACC, and the most important thing to note was that they showed loss of ductal myoepithelial differentiation (Bradley, 2017).

Molecular analysis

The basis for establishing the prognosis of ACC has been the histological subtypes, tumours found at surgical margins, anatomic sites, and metastases. Immunohistochemical and immunocytochemical techniques of p53, bcl-2, P-glycoprotein, glutathione transferase, and topoisomerase staining patterns, and p53 sequence analysis have been used because their association with poor prognosis and resistance to therapy has been proven (Strojan et al., 2017). The aggressive behaviour of ACC is known for its ability to invade and metastasize. One of the factors that regulate these functions is the urokinase-type plasminogen activator and its receptor.

The urokinase-type plasminogen activator receptor participates in several normal cellular processes, but it also influences tumour invasion and metastasis by facilitating the destruction of extracellular matrices. Clinically, cellular expression of the urokinase-type plasminogen activator receptor denotes a worse prognosis for many malignancies. Studies in patients with skull-based ACC have shown that urokinase-type plasminogen activator receptor expression was a negative prognostic factor (Strojan et al., 2017).

Surgical anatomy

Studies have suggested that ACC may originate from mucous-secreting glands, more specifically from the intercalated ducts. Electron microscopy has shown that it arises from cells capable of differentiating into epithelial and myoepithelial cells. Embryological studies have found that there are approximately 250 glands in the hard palate, 100 in the soft palate, and 10 in the uvula. These glands are also associated with the larynx (supraglottis and subglottis), 128 types of HN neoplasms, as well as the nasal and nasopharyngeal tissues (tonsil and posterior tongue) (Strojan et al., 2017). Previous studies have shown that tumour aneuploidy was correlated with more aggressive disease and a poor prognosis (Borras et al., 2015). Recently, an extensive microarray analysis reported the finding that in ACC, the gene encoding the transcription factor SOX4 was overexpressed to a significant extent in normal salivary gland tissue. In addition, there was overexpression of genes encoding AP-2a and AP-2g and genes highly involved in the Wnt/b-catenin signaling pathway were also overexpressed (Bentzen et al., 2010).

Radiotherapy (RT) in Head Neck Cancer (HNC)

Studies have shown that RT plays a key role in the treatment of patients with HNC. Approximately 80% of all HNC patients will receive RT at least once during their disease course (Huang et al., 2021). Reports have indicated that late complications occur three months or more after completion of RT. Many of the late effects occur progressively over time and may eventually have an adverse effect on the quality of life of patients (Jaber, Hassan, Ingafou & Elameen, 2024). The literature has also supported the accepted concept that late side effects resulting from RT may continue in the form of severe acute effects that have not

been completely overcome, such as the relationships between acute mucositis and late dysphagia (Bentzen et al., 2010). Other tissues and structures in the region may, however, also be at risk depending on the tumour site, for example, the jaw or the auditory system (Lombardi et al., 2021).

Most patients are treated with the total curative dose of between 50 and 70 Gray (Gy) that is fractionated in 5-7 weeks, 5 days a week, once a day, consisting of 2Gy per fraction.

Hyperfractionated dosing has been an alternative to the RT technique used to minimize side effects. This strategy makes use of the difference in repair capacities before tumour treatment by dose fractionation, and the conventional treatment time, in which 2 fractions are applied per day, must be maintained. With this type of fractionation, the total dose absorbed by the tumour can be increased, as long as there is no toxicity (Li, Huang, Zheng, Wang & Ge, 2017).

The natural history of salivary gland adenoid cystic carcinoma (SACC), has been described by stating that 10- the year overall survival (OS) rate of patients is about 50%; however, locoregional and distant recurrences commonly occur after a short disease-free interval. With the onset of metastatic disease; however, case series of salivary ACC have suggested a median duration of survival of approximately 3 years. Although complete surgical resection and additional RT have been shown to improve long-term survival, the prognosis of ACC continues to be poor. Therefore, objective prediction of the prognosis is most important in cases of patients with tumour resection and the development of metastasis. To improve patient outcomes, it is important to identify clinical markers that may predict prognosis and response to specific therapies. However, studies have found no established biomarkers that correlate with the outcome and therapeutic response in patients with SACC (Ali et al., 2017).

Studies have shown that the local control rate for free relapse of ACC of the larger salivary glands can be 68% within 5 years and 79% within 10 years. Moreover, they showed that patients who remained without relapse for periods longer than 10 years, and who were submitted to RT alone, had a worse prognosis of survival when compared to the same patients who were submitted to the surgical treatment associated with the adjuvant RT. Solid tumours or those with positive closed margins showed signs of local recurrence (Mantravadi, Moore & Rassekh, 2019).

The sino-nasal ACC, in particular, has a local recurrence rate as high as 37% and its relapse-free survival rate in up to 10 years becomes more evident when adjuvant RT is associated with surgical treatment. For patients diagnosed with ACC in any Tumor, Node, Metastasis classification (TNM) the most indicated treatment so far has, in fact, been surgery followed by RT; and in rare cases, chemotherapy in addition to this combination would be necessary (Mantravadi, Moore & Rassekh, 2019).

Patients with ACC arising from sites close to the skull base (nasopharynx, nasal cavity, and maxilla) have a significantly increased risk of local recurrence. This is related to the difficulty in obtaining safe and clear resection margins at the skull base due to technical difficulties associated with surgery, intracranial extension of the tumour along nerves, and restrictions on the resection limits caused by the proximity of critical neural and vascular structures (Strojan et al., 2017).

Positive surgical margins are strong predictors of poor patient outcomes, and radiation therapy, or the treatment of macroscopic

residual disease is less effective when compared with microscopic disease (Strojan et al., 2017).
Pathologic findings have also been correlated with local recurrence rates: Positive resection margins in ACC of the HN are significantly associated with an increased risk of local recurrence. In addition, tumours located close to the cranial base, tumour grade, and an increased solid component have been associated with an increased risk of local recurrence. Grade I tumours have also been associated with early recurrence (>1 year) and an earlier risk for the development of distant metastases. The extent of a sample taken from the specimen will determine the detection of positive resection margins and perineural invasion of ACC, which may vary significantly (Strojan et al., 2017).
Additional prognostic information can be obtained using Ki-67 and p53 staining. Cytogenetic and gene expression analysis may play an increasing role as additional prognostic factors. However, studies evaluating the efficacy of chemotherapeutics and molecular therapies continue to show disappointing results (Morita et al., 2021). The clinical course of the disease can be surprisingly heterogeneous, with some patients surviving decades and others surviving only months. In one series, the survival of patients with initial recurrence manifesting as distant metastasis ranged from 5 months to 12 years (Morita et al., 2021).
The RT is the mainstay strategy for the treatment of HN cancer. Intensity-modulated X-ray therapy (IMXT) alone is the current standard for Stage I and II HN. For Stage III and IV A/B diseases, concurrent chemotherapy should be provided in addition to IMXT. However, optimal treatment for locally recurrent HN after previous definitive doses of RT is still lacking. Various techniques including brachytherapy, IMXT, stereotactic radiosurgery or RT (SRS or SBRT) have been used in the management of locally recurrent HN. Carbon ion radiotherapy (CIRT) offers potential physical and biological advantages over photon and proton RT (Kong et al., 2016). According to one study, the inverted dose profile of particle beams and their greater energy deposition within the Bragg peak, have made it possible to deliver precise dose(s) to the target volume(s) without exposing the surrounding organs to the risk of receiving extra doses. In addition, CIRT provides an increased relative biological effectiveness (RBE) when compared with photon and proton RT. These advantages may translate into improved outcomes after irradiation in terms of disease control in radio-resistant and previously treated, recurrent malignancies. Reports on the treatment of radio-resistant malignancies in the HN region such as melanoma, sarcoma, and ACC have demonstrated superior local control rates resulting from CIRT when compared with photon irradiation. Thus, patients with recurrent HN are likely to benefit from the enhanced biological effectiveness of carbon ions. As there is no effective retreatment strategy for locally recurrent HN, CIRT offers an ideal alternative to conventional X-ray irradiation (Mikoshiba et al., 2022).

Discussion

Treatment of locally recurrent HN after High-dose radiation (HDR) is challenging for several reasons. The HDR areas of the initial RT for the primary disease usually encompass not only the gross tumour volume but also the surrounding OARs such as the nasopharyngeal mucosa, temporal lobes of the brain, brain stem, and optic nerve/chiasm for subclinical disease. A substantial portion of the temporal lobes of the brain and most parts - if not the entire nasopharynx may be covered by an HDR

of > 66 Gy especially in T3 or T4 HN (Mikoshiba et al., 2022). The incidence of severe adverse effects (SAEs) increases significantly when the combined radiation dose from initial and re-irradiation exceeds 100 Gy. Thus, re-irradiation to a dose of 60Gy or more may cause long-term radiation-induced SAEs such as brain necrosis and mucosal ulceration and necrosis. Mucosal ulceration and necrosis are devastating SAEs – capable of directly causing significant loss of quality of life, even death due to infection or massive haemorrhage of the internal carotid artery. Local recurrence after HDR photon may be secondary to photon cancer cells that survived the initial course of treatment. HN patients might also suffer local failure due to a marginal miss after 2D or 3D-conformal RT (3D-CRT). The prevailing use of IMXT has significantly improved the treatment outcome, especially in local and regional disease control. The use of advanced diagnostic technology such as MRI and PET/CT together with IMXT has been expected to minimize the instances of marginal misses of the primary disease and neck adenopathy. However, approximately 10~15% of patients who completed IMXT of 70Gy still failed locally. Therefore, it is reasonable to postulate that subgroups of cells within the disease may be more resistant to photon RT. Whether these features of radio-resistance are caused by hypo-oxygenation, inherently resistant clones, or the presence of cancer stem cells (CSCs) or stem cell-like cells remains to be investigated. Nevertheless, their characteristics of radio-resistance to X-ray-based IMXT could result in a more dismal outcome after re-irradiation using IMXT. Salvage radiation treatment using phototherapy with the same or lower dose, usually in the range of 60~70Gy at standard fractionation, may not produce sufficient long-term disease control. Therefore, previous treatment using IMXT in HN poses additional challenges when re-irradiation for local recurrence has to be performed because this clinical scenario requires potential radio-resistant disease to be targeted while it is in the setting of OARs that have already received significant doses (Mikoshiba et al., 2022).

When we specifically consider the local recurrence of salivary gland tumours, irradiation or, in some cases, re-irradiation is an option for nonsurgical treatment. If re-irradiation is being considered, patient selection is a critical aspect, because of the toxicity of this treatment, and the likelihood of the patient having resistant disease, especially in cases of tumour recurrence within six months after the first course of treatment. RT for recurrent disease is generally carried out with conventional external beam RT using photons. Alternative approaches include the following: High linear energy transfer RT (e.g., protons, neutrons, carbon ions) (Nishida, Kusaba, Kawamura, Oyama & Daa, 2023). intraoperative RT (combined with salvage surgery) and brachytherapy offer additional options for salvage therapy. These options are, however, usually reserved for patients who previously received external beam RT (Skalova et al., 2021). RT combined with local hyperthermia or concurrent chemoradiotherapy may play a role in the treatment of some locally advanced or recurrent salivary gland tumours, but experience is limited, and these continue to be investigational approaches (Seethala et al., 2019).

Particle therapy such as a proton or carbon-ion radiation therapy (PRT or CIRT) provides distinct physical characteristics that include: a sharp lateral penumbra; very low energy deposition within the entry path prior to the Bragg peak formed by the steep dose deposition; and, a sharp dose fall-off after the Bragg peak, thus providing a dose delivery

within a finite range. The depth of the Bragg peak is determined by the beam energy. In radiation therapy of the HN area, it is crucial to spare the normal surrounding tissues, especially for patients who have completed a previous course of HDR. Several studies have reported superior dose distributions using particle therapy for primary or recurrent HN with acceptable clinical outcomes (Seethala et al., 2019). In addition to its superior physical properties, carbon ion is a high LET modality and the relative biological effectiveness (RBE) of CIRT is significantly higher than those features of photon and proton radiation. The value of RBE is 3~5 for carbon ion depending on the tissue type and end point of study. It has been suggested that more damage from high LET radiation occurs in the form of direct DNA double-strand breaks, which are more difficult to repair (Seethala et al., 2019). Therefore, improved clinical results could be expected after high-LET radiation such as CIRT, especially for photon-resistant cancer cells. According to the convention with CIRT (and other particle-based modalities), we will account for the RBE and LET differences between CIRT and photon RT and report our CIRT doses in terms of Gray Equivalents (GyE), which refer to the biologic equivalent doses of photons.

Improved treatment results from CIRT have been demonstrated for a number of disease entities including chordoma/chondrosarcoma of the skull base, melanoma and ACC of the HN area (Seethala et al., 2019). CIRT is routinely offered to patients with tumor entities at the Heidelberg Ion-Beam Therapy Center (HIT), in Germany and the National Institute of Radiological Science (NIRS), in Japan. Safety of CIRT relative to critical OARs as optical nerve/chiasm, brain, brainstem, or spinal cord, has also been reported. Particle therapy has been used in the re-treatment of local recurrence of HN tumours. In a retrospective study of 16 locally recurrent HN patients who were re-irradiated with PT, the authors found that a dose of 61Gy or higher (in 1.8-2.0 Gy per daily fraction) produced a local control of 60% vs. 38% for those who received a lower total dose (P=0.17) (Seethala et al., 2019). The overall survival (OS) at 24 months was 50%. With a cumulative dose of 133.5 Gy (range, 110-148) for both the initial and repeated radiation, 2 out of 9 (22.2%) surviving patients developed grade 3 or 4 late toxicity (osteo- and mucosal necrosis) which were successfully treated. The doses to the optic chiasm, surface and centre of the brainstem were 60.0 Gy, 60.0 Gy, and 57.0 Gy, respectively, but no patient experienced any neurological deficit. The BED2 and BED9 of the re-irradiation regimen were 116.3 GyE and 61.2 GyE, respectively for late responding tissues and tumour tissue.

A more recently published series from HIT studied a group of 28 patients with local recurrence after initial RT. Eighteen patients had a base of skull tumours and the majority were treated with carbon re-irradiation to 51GyE in 3 GyE daily fractions over the course of 17 days, 7 days a week (range, 42~60 GyE). Three of the 18 patients received 2 courses of RT prior to the re-irradiation sessions, using carbon for their recurrence. Grade 1 or 2 early or late toxicity was observed in only 5 patients. No patient developed Grade 3 or 4 early or late toxicities. An alpha/beta value of 2 was used for the endpoint late toxicity to the normal tissue. Therefore, the BED2 and BED9 were 127.5 GyE and 68 GyE, respectively. With the superior physical and biological properties of CIRT, it is reasonable to postulate that CIRT may produce promising outcomes in locally recurrent HNs after IMXT. In this current phase I/II study, we first intend to define the maximal tolerated dose (MTD) of CIRT for re-irradiation of HN patients with local failure after their

initial course of photon-based intensity-modulated RT, then test the efficacy of the defined MTD (Seethala et al., 2019).

Conclusion

Optimal treatment of ACC has not yet been fully established. Although the majority of authors advocated the use of surgical excision and postoperative RT, some series found no statistically significant difference between patients treated with combination therapy and those treated with surgery alone. Careful tumour staging and grading with documentation of perineural invasion and margin status continue to be important prognostic tools. There may be an increasing role for cytogenetic and gene expression analysis as additional prognostic factors. Once metastatic disease has occurred, especially in the lungs, many patients can survive for long periods. Nevertheless, up to now, ACC has been incurable and most patients will eventually succumb to local recurrence, distant metastasis, or both. The clinical course of the disease can be surprisingly heterogeneous with some patients surviving decades and others surviving only months. Clearly more accurate measures of prognosis are needed, along with studies examining the use of molecular and genetic changes as therapeutic targets.

Lista de Abreviações:
3D – CRT - 3D-conformal RT, ACC - Adenoid Cystic Carcinoma, AJCC – American Joint Commitee on Cancer, CIRT - Carbon Ion Radiotherapy, CSC - Cancer Stem Cells, GyE - Gray Equivalents, HDR - Hight-Dose Radiation, HN – Head and Neck, HIT - Heidelberg Ion-Beam Therapy Center, IMXT - Modulated X-Ray Therapy, NIRS - National Institute of Radiological Science, OS - Overall Survival, PRT or CIRT - Proton or Carbon-ion Radiation Therapy, RBE - Relative Biological Effectiveness, RT – Radioterapia, SACC - Salivary Gland Adenoid Cystic Carcinoma, SAE - Severe Adverse Effects, SRS or SBRT - Stereotactic Radiosurgery or Radiotherapy, TNM - Tumor, Node, Metastasis classification.

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