Review Article

Intensity Modulated Radiotherapy, Brachytherapy & Intensity Modulated Proton Therapy in Oral Cancers: A Narrative Review

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Abstract

Background: In India, oral cancer is among the most prevalent malignancies, yet it is a rare disease worldwide in Western nations. Owing to its elevated fatality rate, prompt diagnosis is crucial. Treatment approaches for oral squamous cell carcinomas include surgery, radiotherapy and adjuvant chemotherapy. Each of these modalities is undergoing advancement with time. Advanced radiotherapy modalities stand out because they precisely target cancer cells with less likely damage to nearby healthy tissues. This review is an overview of Intensity Modulated Radiotherapy, Brachytherapy and Intensity Modulated Proton Therapy. Future studies on the effects of various treatment options for patients with cancer should also investigate the impact on the patient's quality of life and well-being.

Methodology: A literature search of peer-reviewed publications was undertaken to identify original peer-reviewed works about the use of radiation for squamous cell carcinomas in the head and neck region. Search words like intensity-modulated radiation therapy, brachytherapy, proton therapy and oral squamous cell carcinomas were entered together using nesting and Boolean operators (e.g. AND, OR, NOT). Reference lists from included articles were cross-checked to identify additional articles. Articles published from 1995 to 2024 with free full text available on PubMed and Google Scholar, restricted to the English language and human subjects were included. The full bibliographies of identified articles were reviewed and case reports and clinical trials were selectively removed. Observational series devoid of disease-specific outcomes as measured by progression-free survival or overall survival were also excluded. An interpretive synthesis of the available publications was then presented.

Keywords: Intensity Modulated Radiotherapy, Brachytherapy, Intensity Modulated Proton Therapy, Oral squamous cell carcinoma

Introduction:

One of the top three cancers in the nation and a significant issue on the Indian subcontinent is oral cancer.[1] The clinical definition of "oral cancer", is defined by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) in the tumour node metastasis (TNM) staging classification. This includes Oral Squamous Cell Carcinomas (OSCC) originating from the mucosal lip, anterior two-thirds of the tongue (oral tongue), buccal mucosa, floor of mouth, hard palate, lower & upper alveolus and gingiva, and the retromolar trigone. Surgery as a single modality, radiation therapy [brachytherapy and/or External Beam Radiation Therapy (EBRT)], or different combinations of these modalities with or without systemic therapy (chemotherapy and/or target drugs) are all used to treat OSCC. The management of the condition and the intended functional and aesthetic results are taken into account when choosing a course of treatment.[2]

Typically, surgery is the primary form of OSCC treatment.[3] In general, three scenarios call for the use of EBRT, either with or without chemotherapy: a) as an adjuvant to primary surgery to improve Loco-Regional Control (LRC) for cases with unfavourable pathological features; b) as primary treatment for cases that cannot tolerate or are not fit for surgery; and c) as salvage treatment in the setting of persistent or recurrent discomfort. When treating patients with early disease and a well-defined primary tumour, brachytherapy can be used alone or in conjunction with surgery in cases with positive resection margins.[2]

For patients with unfavourable pathological features, Postoperative Radiotherapy (PORT) or Post-Operative Concurrent Chemo-Radiotherapy (POCRT) have been shown to improve locoregional control (LRC) and survival in several clinical trials.[4–6]. General indications for PORT include T3 or T4 tumour; compromised surgical resection margins (<5 mm from the inked surface of the specimen); the presence of Lymphovascular Invasion (LVI) and/or Peri-Neural Invasion (PNI); and positive lymph nodes with or without extracapsular invasion (ECE).[4,7]

Radiotherapy:

Like surgery, radiotherapy is a loco-regional kind of care. When deciding on the management of oral cavity tumours, one must consider both functioning and cosmesis; therefore, a multidisciplinary team must make the decision. These malignancies are classified as early-stage, locally progressed, and metastatic for prognosis and treatment.[8]

The first stage in designing a radiation treatment is determining the target precisely. The area to be treated is defined concerning bony landmarks. This is followed by the creation of a brick-shaped centre zone with high dosage distribution using many overlapping beams. Planning and delivering radiation therapy are undergoing significant change. The development of advanced three-dimensional Radiation Treatment Planning (3D-RTP) and Computer-Controlled Radiation Therapy (CCRT) delivery systems is largely due to ongoing advancements in computer hardware and software.[9–11] Therefore, it is now possible to implement three-Dimensional Conformal Radiation Therapy (3D-CRT) to minimize radiation exposure to nearby normal structures while simultaneously conforming the prescribed dosage's spatial distribution to the 3D target volume, which consists of malignant cells plus a margin for spatial uncertainty. A collection of fixed radiation beams that are formed using the target volume projection is often used to deliver 3D-CRT. Normally, the radiation beams are the same intensity throughout the field; but, when necessary, small devices like wedges or compensating filters can be used to vary the intensity of the beams. However, a new kind of conformal planning and delivery technology has been emerging to replace conventional 3D-CRT. Intensity-Modulated Radiation Treatment (IMRT), a novel kind of 3D-CRT, is based on the use of optimized non-uniform radiation beam intensities incident on the patient.[12,13] Inverse planning or automated optimization 3D-RTP systems, which employ computer optimization techniques to help establish the distribution of intensities across the target volume, are frequently used to develop IMRT treatment plans.[14]

Intensity-modulated radiotherapy

IMRT is a type of 3-dimensional conformal radiotherapy (3D-CRT) with an advanced delivery of external beam irradiation. 3D-CRT/IMRT is an addition and a significant modification to the current radiation oncology procedure in practice. For instance, 3D-CRT/IMRT necessitates the use of 3D treatment planning tools such as MRI and CT, to define target volumes and organs at risk in three dimensions by contouring cross-sectional images slice-by-slice. Furthermore, IMRT mandates that the doctor specify the treatment goals in a precise, quantitative manner. As of right now, most IMRT techniques will require more time and effort by radiation therapists, medical physicists, doctors, and dosimetrists because the technologies for IMRT planning and delivery are not yet reliable enough to offer automated solutions for every disease site.[14] Target volumes with complicated or concave geometries that are close to radiosensitive normal structures are especially valuable.[15] In comparison to conformal radiation therapy, it includes two important features: non-uniform radiation beam intensity and inverse planning.

Non-uniform radiation beam intensity: Unlike other radiotherapy procedures, which use uniform radiation intensity, variable radiation intensity is generated across each beam. It is possible to create an incredibly intricate pattern since each beam is divided into hundreds of beamlets, each with a different intensity level. A highly conformal dose distribution can be created by using several beams, which enables accurate contouring to a curved target and further spares normal tissue.[16]

Benefits of IMRT include increased normal tissue sparing, dose painting, dose escalation, improved target conformity, especially for concave target volumes, and the ability to make up for missing tissue. The following are some drawbacks of IMRT: longer target and organ outlining times for clinicians; a comprehensive quality assurance programme is required; longer machine treatment times; longer initial planning times; and higher doses of radiation to the entire body.

Inverse planning: The use of computerised inverse planning is one of the main characteristics that sets IMRT apart from other radiation methods. In conformal radiotherapy, the quantity, form, and orientation of the beams are determined in advance and depend on the treatment planner's expertise. On the other hand, inverse planning outlines the intended result in terms of the dose limitations for normal structures and cancer. Then, to discover a configuration that best fits the intended plan, the computer system modifies the beam intensities. The patient's path is followed by each beamlet to create the initial dose distribution. Next, a single beamlet's weighting is slightly adjusted; if this modification improves the distribution, it is approved. This process is repeated for all beams for one cycle (iteration) and should result in a better plan. The iterative process is repeated for several cycles until no improvement is seen. This results in an optimal intensity in each beam to produce a defined dose distribution.[16] The dose that must be administered to reach the target volume and the dose limitations for the organs that are at risk must be specified by the clinician. Tumours located close to radiosensitive structures frequently need extremely intricate treatment regimens using conventional and conformal methods. Reducing the dose to the tumour can be necessary to avoid unacceptably serious late consequences. The treatment course must often be divided into multiple phases, with distinct field layouts for each phase. By enabling "dose-painting," or the assignment of various dosage targets for therapy, IMRT enables the purposeful inhomogeneity of dose distribution.

IMRT delivery: The two most common methods are segmental IMRT and dynamic IMRT which use Multi-Leaf Collimators (MLC). Tomo therapy: IMRT can also be delivered with a fan beam. As the gantry rotates around the patient, the beam is collimated to a narrow slit and then changed with moving leaves. Due to the target volume's intricacy and concavity as well as the close vicinity of radiosensitive dose-limiting structures in the head and neck regions, these tumours are benefiting from IMRT.[17]

Brachytherapy

Brachytherapy involves the placement of radioactive sources in or close to the target volume. Technologies like 3D visualization, and dose optimization with the help of CT and MRI-compatible systems have added to the ultimate goal of radiotherapy which is "Maximum dose to tumour and minimum dose to surrounding normal structures".[18] The direct application of radioactive sources to cancer is known as Brachytherapy (BT). Steep dose gradients, high-dose radiation delivered to the target volume centre, and the preservation of neighbouring healthy tissues are the distinguishing features of this approach. Treatment outcomes were equivalent to surgery when using Low-Dose-Rate (LDR) BT and manual after-loading in the treatment of early-stage oral cancer. As a result of improved surgical methods, the transition from low-dose-rate (LDR) to High-Dose-Rate (HDR) BT (which carries a higher risk of problems), and developments in EBRT, interest in BT as a primary treatment for oral cancer has decreased recently. Currently, the postoperative situation is where BT is most often used since it offers a higher quality of life and greater dosage conformance than EBRT. Postoperative BT can be used in tandem with elective neck dissection or EBRT to treat larger or deeper tumours, or it can be used alone in cases of early-stage (T1N0) malignancies. When it comes to lip carcinoma in elderly patients and tumours with unfavourable locations, BT produces great results. In locations that have already been exposed to radiation, BT is a useful salvage treatment for local recurrences. Brachytherapy has many benefits, but it's a complicated procedure that needs careful execution and close collaboration between the radiation oncologist, physicist, and surgeon.[19] Several significant drawbacks of BT include the implantation process's invasiveness and the tumours' maximum size (≤4 cm) that can be treated with BT. However, BT is still the most conformal type of radiation; current research indicates that BT is superior to intensity-modulated RT in terms of sparing organs at risk of oral cancer.[19,20]

Pierquen and Dutreix in the 1960s developed the Paris system of implantation and dosimetry, used to date. This period from the 1950s to the 1980s is widely considered the "golden age of brachytherapy".[21]

Inactive applicators are implanted first, and then radioactive sources are inserted, in the two-step manual after-loading procedure. For many years, the mainstay of brachytherapy was low-dose-rate (LDR) BT (0.3–0.9 Gy/hour). Total dosages for LDR BT vary from 60 to 70 Gy, given over a period of around one week. High-dose-rate BT (HDR-BT) with automated after-loading began to supplant LDR BT in the 1990s. Compared to LDR BT, HDR-BT offers many benefits, such as a more accurate dose distribution, a shorter treatment duration, a better radiation safety profile, and the ability to treat more patients. When it came to intraluminal therapy of bronchial and oesophageal stenosis and intracavitary treatment of gynaecological malignancies, HDR-BT produced outcomes that were on par with LDR BT. However, because of the possible increased risk of problems, there have been reservations regarding the use of HDR-BT for interstitial applications. The decrease in interest in BT over the past 20 years can be explained by this worry as well as the introduction of newer and more potent EBRT procedures. When used as the only treatment modality, postoperative technique, and reirradiation approach, BT has been shown to have excellent local control rates and to have acceptable side effects. Because LDR BT produces such excellent results, it is used all over the world. HDR-BT has made it possible for medical personnel to minimise radiation exposure since the development of technology. Numerous cancers, including gynaecological, breast, and prostate cancers, have been treated with this therapy. HDR BT is still a valuable therapy option for oral cancer.[22]

Brachytherapy for Tongue, floor-of Mouth and Lip Cancers: The head and neck cancer treatment known as LDR BT uses iridium wires or hairpins inserted through plastic tubes. When it comes to oral cancer, BT has been recommended as a monotherapy for squamous cell carcinoma in stages I–II, and in conjunction with EBRT for more advanced cases including oropharyngeal tumours. Several studies have demonstrated that when BT is used as the primary treatment for early-stage tongue cancer, either alone or in conjunction with low-dose EBRT, the Local Control (LC) rates are superior. This is primarily because BT can provide large radiation doses quickly. As a result, definitive BT was advised as the first line of treatment for tumours in stages T1N0 and T2N0. Most patients had elective neck dissection (END) after interstitial irradiation; EBRT was added in cases where there was nodal invasion. Research conducted in the 1970s revealed that the five-year local cancer rates for oral malignancies that were surgically treated ranged from 81% to 85% for T1 tumours and from 77% to 85% for T2 tumours.(23,24)

In the late 1990s, HDR-BT and automatic after-loading procedures essentially supplanted manual after-loading and LDR BT in the majority of radiation departments. The lower therapeutic ratio can be explained by the fact that HDR-BT (dose rate ≥ 12 Gy/h) has a stronger biological effect than LDR BT, and that effect is greater in slower-acting normal tissues than in cancer tissue. That's the reason a fractionated technique is needed for HDR-BT. For a given amount of cancer control, moving from LDR to HDR generally increases the chance of adverse effects, especially in interstitial applications. To obtain the same effects on the tumour and normal tissues as obtained with LDR BT, it is crucial to choose the ideal number of fractions and total dose of HDR-BT. The goal of the early 1990s was to replicate the biological effects of continuous LDR-BT using the same stepping source technology as high-dose radiation therapy HDR-BT. The entire dosage is administered in the same amount of time as continuous LDR treatment, but it is administered in several smaller portions, or pulses, usually once every hour and sometimes as much as once every four hours.

The use of LDR BT in oral cancer has been the subject of numerous published investigations. On the other hand, there is significantly less material on HDR BT for this indication now accessible. For HDR BT, fractionation regimens usually vary from 3 Gy to 6 Gy per fraction. Early HDR-BT findings in oral cancer were inconclusive; reported rates of osteoradionecrosis (3–20%) and local control (53–94%) varied greatly. Treatment results increased dramatically over time as treatment facilities accumulated more expertise and guidelines for the best fractionation in HDR-BT were created.[25] According to the findings of two randomised clinical trials (Inoue et al. and Yamazaki et al.) conducted on patients with oral cancer, the outcomes of both LDR and HDR-BT were comparable.(25,26) According to a meta-analysis of studies comparing these two therapy modalities for oral cancer, HDR-BT and LDR BT were shown to be similar, suggesting that HDR-BT might be used as a standard treatment for early-stage oral cancer.(27) For the majority of cases, surgery is currently thought to be superior to BT due to significant advancements in surgical procedures in recent years.(28) Individuals who receive interstitial BT alone for tumours larger than 2 cm are especially vulnerable to local recurrence. Furthermore, as the implant volume grows, so does the frequency of osteonecrosis and soft tissue necrosis.(29) For the final treatment of SCC of the lip, brachytherapy offers good local control and acceptable aesthetic outcomes. Comparable 5-year LC rates (around 95%) and 5-year OS rates (between 70 and 90%) are produced by LDR BT and HDR-BT.(27,28,30,31)

Improvements in BT Techniques: While surgical advancements have improved the prognosis for early-stage oral cancer, BT, surgery's historical competitor, is also continuously improving and standardising treatment protocols. The use of magnetic resonance imaging (MRI) to determine the size of the tumour was given priority in the 2017 GEC ESTRO recommendation. This is because MRI makes it easier to determine the clinical target volume and lowers the chance of local recurrences following brachytherapy for squamous cell carcinomas of the head and neck. An adjuvant BT proposal with dose-volume histogram limitations was released in 2021 by the GEC ESTRO Working Group to reduce the danger of soft tissue necrosis and post-radiation osteoradionecrosis.(32)

Proton Therapy

Proton Therapy stands out because of the special physical characteristics of charged particles, a patient can receive a steep dose gradient with a lower integral dose in a proportion that can significantly lessen dose-related toxicity. A particle accelerator that can be used for medical purposes accelerates a concentrated beam of protons. Protons' two primary advantages over photons in terms of dosimetric superiority are (1) no exit dosage beyond the target and (2) a sharper lateral dose distribution as a result of their heavier mass. Because protons are charged, there is a sudden rise in dosage at the end of the particle range, a phenomenon known as the Bragg peak phenomenon. Techniques like active scanning or passive scattering can be used to administer proton therapy. The passive scattering method, which is similar to 3D photon treatment, employs scattering foils to spread out the proton beam and then uses brass apertures to conform it laterally. Similar to how photon therapy operated before the development of multi-leaf collimators, range compensators are employed for depth modulation. This approach is less flexible than active scanning since it requires the labour-intensive fabrication of equipment tailored to each patient, generates secondary neutrons, and limits the potential for adaptive replanning if cancer spreads or anatomical changes throughout the treatment course. On the other hand, intensity-modulated proton treatment, or active scanning, depends on the magnetic characteristics of protons. To treat the various layers of the tumour, a tiny proton beam is created, its energy is adjusted, and magnets are utilised to deflect and shape the beam to the desired volume. Nowadays, IMPT is the most popular type of proton treatment, and it is available in all newly built facilities. A multifield optimisation technique that permits the simultaneous optimisation of all spots from all fields is used in the treatment planning process for head and neck cancers.(33)

Protons' sensitivity to geometrical and physical errors is a disadvantage of their dosimetric superiority, which must be taken into consideration both before and during treatment[32,33]. Before the plan is authorised during the planning phase, it is important to evaluate how resistant the optimisation is to changes in patient setup, anatomical changes brought on by tumour response or weight fluctuations, beam range variations, and patient mobility during treatment.[34]

Because proton beams provide a fast fall-off dose, they are therefore the best option for treating tumours that have spread intracranially or that are situated in sensitive regions such as the cavernous sinus, periorbital region, or skull base. A delimited three-dimensional (3D) target volume can be covered by Spread-Out Bragg Peak modulated (SOBP) fields on CT by using scattering foils, energy modulation techniques, and brass apertures[34] Passively Scattered Proton Therapy (PSPT), a type of RT technique, has been extensively researched and utilised for both primary and recurrent HNCs.[35–41]

IMPT is a more advanced and intricate technical method of providing RT. It is also frequently referred to as "pencil beam" or "active scanning." The accelerator produces proton "pencil" beams that are controlled to treat tumours in layers of spots at different depths by adjusting the energy (local penetration), magnetic deflection (off-axis coverage), and number of protons (local dose deposition).[42] In contrast to IMRT, which uses mechanical multi-leaf collimators and different beam configurations (or arcs) to create a conformal dose distribution, IMPT uses electromagnetic control of the pencil beam to accomplish similar target coverage while lowering the integral dose amount. For HNC therapies that aim for dose escalation while protecting organs at risk (OARs), IMPT appears more promising than IMRT. [43]

Due to the superficial location of HNC tumours, range shifters or patient-specific bolus must be used with IMPT. Alternatively, multifield optimisation (MFO-IMPT) can be used to create high-quality plans without the need for range shifters.[33,44–46] Treatment of HNCs is now usually advised to use MFO-IMPT plans, which can be created using three to four fields (usually a left and right anterior oblique beam and a single posterior beam ± a vertex beam) that are optimised simultaneously for all spots from all fields using multi-criteria inverse optimisation algorithms.[46, 47] IMPT can also be used to create patient-specific apertures for a more acute lateral penumbra and additional OAR dosage reductions.[47]

When compared to IMRT or PSPT, IMPT plans have been demonstrated to produce both dosimetric advantages and clinically acceptable treatment-related toxicities[31,43]. However, it is important to recognise that this technology has significant limitations. First off, uncertainties in particle range and anatomical changes can greatly affect IMPT. These uncertainties can be caused by intra-fractional organ motion, inter-fractional variations in patient positioning, or changes in target volume during treatment (such as tumour regression or patient weight loss).[48] When using IMRT planning, it is possible to ensure proper target coverage by the specified dosage by using simple margin expansions to allow for setup errors and anatomical changes. Through compensator smearing and aperture widening, PSPT can take clinical uncertainty into account.[48] More work has to be put into developing strong optimisation techniques and using frequent imaging to confirm treatment regimens and/or initiate adaptive planning while a patient is receiving therapy for IMPT.[34,49–52] The precision of IMPT planning may be impacted by limitations in proton beam energy switching time, scanning-spot optimisation techniques, and Relative Biological Effectiveness (RBE).[43,53–55] All of these, however, are now being researched, including the creation of optimisation led by linear energy transfer and innovative techniques for smoothly combining beam orientation optimisation with scanning-spot optimisation.[53,56–58] For IMPT to be successfully used in the clinic, effective patient-specific quality assurance processes must be established and standardised.[34,59]

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References :

1. Elango JK, Gangadharan P, Sumithra S, Kuriakose MA. Trends of head and neck cancers in urban and rural India. Asian Pac J Cancer Prev 2006;7(1):108–12.
2. Huang SH, O Sullivan B. Oral cancer: Current role of radiotherapy and chemotherapy. Med Oral Patol Oral Cir Bucal 2013;e233–40.
3. Bessell A, Glenny AM, Furness S, Clarkson JE, Oliver R, Conway DI, et al. Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. Cochrane Database Syst Rev 2011;(9):CD006205.
4. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck 2005;27(10):843–50.

5. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative Concurrent Radiotherapy and Chemotherapy for High-Risk Squamous-Cell Carcinoma of the Head and Neck. New England Journal of Medicine 2004;350(19):1937–44.
6. Shrime MG, Gullane PJ, Dawson L, Kim J, Gilbert RW, Irish JC, et al. The Impact of Adjuvant Radiotherapy on Survival in T1-2N1 Squamous Cell Carcinoma of the Oral Cavity. Arch Otolaryngol Head Neck Surg 2010;136(3):225.
7. Peters LJ, Goepfert H, Ang KK, Byers RM, Maor MH, Guillamondegui O, et al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: First report of a prospective randomized trial. International Journal of Radiation Oncology*Biology*Physics 1993;26(1):3–11.
8. Kirthi Koushik AS, Charith Alva R. Radiotherapy in Oral Cancers: Current Perspective and Future Directions. In: Oral Cancer - Current Concepts and Future Perspectives. IntechOpen; 2022.
9. Brahme A. Optimized radiation therapy based on radiobiological objectives. Semin Radiat Oncol 1999;9(1):35–47.
10. Fraass BA, McShan DL, Kessler ML. Computer-controlled treatment delivery. Semin Radiat Oncol 1995;5(2):77–85.
11. Tsai JS, Wazer DE, Ling MN, Wu JK, Fagundes M, DiPetrillo T, et al. Dosimetric Verification of the Dynamic Intensity-Modulated Radiation Therapy of 92 Patients. International Journal of Radiation Oncology*Biology*Physics 1998;40(5):1213–30.
12. Verellen D, Linthout N, Van Den Berge D, Bel A, Storme G. Initial experience with intensity-modulated conformal radiation therapy for treatment of the head and neck region. International Journal of Radiation Oncology*Biology*Physics 1997;39(1):99–114.
13. Low DA, Chao KSC, Mutic S, Gerber RL, Perez CA, Purdy JA. Quality assurance of serial tomotherapy for head and neck patient treatments. International Journal of Radiation Oncology*Biology*Physics 1998;42(3):681–92.
14. Intensity-modulated radiotherapy: current status and issues of interest. International Journal of Radiation Oncology*Biology*Physics 2001;51(4):880–914.
15. IMRT Collaborative Working Group. Intensity-modulated radiotherapy: current status and issues of interest. Int J Radiat Oncol Biol Phys 2001; 51(4): 880–914.
16. Webb S. The physical basis of IMRT and inverse planning. Br J Radiol 2003;76(910):678–89.
17. Chui C, Chan MF, Yorke E, Spirou S, Ling CC. Delivery of intensity-modulated radiation therapy with a conventional multileaf collimator: Comparison of dynamic and segmental methods. Med Phys 2001;28(12):2441–9.
18. Mazeron JJ, Ardiet JM, Haie-Méder C, Kovács G, Levendag P, Peiffert D, et al. GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinomas. Radiotherapy and Oncology 2009;91(2):150–6.
19. Tuček L, Vošmik M, Petera J. Is There Still a Place for Brachytherapy in the Modern Treatment of Early-Stage Oral Cancer? Cancers (Basel) 2022;14(1):222.
20. Chargari C, Deutsch E, Blanchard P, Gouy S, Martelli H, Guérin F, et al. Brachytherapy: An overview for clinicians. CA Cancer J Clin 2019;69(5):386–401.
21. Pierquin B, Dutreix A, Paine CH, Chassagne D, Marinello G, Ash D. The Paris System in Interstitial Radiation Therapy. Acta Radiol Oncol Radiat Phys Biol 1978;17(1):33–48.
22. YamazakI H, Yoshida K, Yoshioka Y, Shimizutani K, Furukawa S, Koizumi M, et al. High dose rate brachytherapy for oral cancer. J Radiat Res 2013;54(1):1–17.
23. Whitehurst JO, Droulias CA. Surgical Treatment of Squamous Cell Carcinoma of the Oral Tongue: Factors Influencing Survival. Archives of Otolaryngology - Head and Neck Surgery 1977;103(4):212–5.
24. Spiro RH, Strong EW. Epidermoid carcinoma of the mobile tongue. The American Journal of Surgery 1971;122(6):707–10.
25. Inoue T, Inoue T, Yoshida K, Yoshioka Y, Shimamoto S, Tanaka E, et al. Phase III trial of high- vs. low-dose-rate interstitial radiotherapy for early mobile tongue cancer. International Journal of Radiation Oncology*Biology*Physics 2001;51(1):171–5.
26. YAMAZAKI H, INOUE T, YOSHIDA K, YOSHIOKA Y, FURUKAWA S, KAKIMOTO N, et al. Brachytherapy for Early Oral Tongue Cancer: Low Dose Rate to High Dose Rate. J Radiat Res 2003;44(1):37–40.

27. Johansson B, Karlsson L, Hardell L, Persliden J. Clinical Investigations Long term results of PDR brachytherapy for lip cancer. J Contemp Brachytherapy 2011;2:65–9.
28. Guinot J, Arribas L, Vendrell JB, Santos M, Tortajada MI, Mut A, et al. Prognostic factors in squamous cell lip carcinoma treated with high-dose-rate brachytherapy. Head Neck 2014;36(12):1737–42.
29. Grabenbauer GG, Rödel C, Brunner T, Schulze-Mosgau S, Strnad V, Müller RG, et al. Interstitial Brachytherapy with Ir-192 Low-Dose-Rate in the Treatment of Primary and Recurrent Cancer the Oral Cavity and Oropharynx. Strahlentherapie und Onkologie 2001;177(7):338–44.
30. Treatment of the carcinoma of the lip through high dose rate brachitherapy. Finestres-Zubeldia F 1 , Guix-Melcior B , Cloquell-Damian A , Chimenos-Küstner E , Tello-Luque JI.
31. Guibert M, David I, Vergez S, Rives M, Filleron T, Bonnet J, et al. Brachytherapy in Lip Carcinoma: Long-Term Results. International Journal of Radiation Oncology*Biology*Physics 2011;81(5):e839–43.
32. García-Consuegra A, Gimeno Morales M, Cambeiro M, Tagliaferri L, Kovacs G, Van Limbergen E, et al. Dose volume histogram constraints in patients with head and neck cancer treated with surgery and adjuvant HDR brachytherapy: A proposal of the head and neck and skin GEC ESTRO Working group. Radiotherapy and Oncology 2021;154:128–34.
33. Frank SJ, Cox JD, Gillin M, Mohan R, Garden AS, Rosenthal DI, et al. Multifield Optimization Intensity Modulated Proton Therapy for Head and Neck Tumors: A Translation to Practice. International Journal of Radiation Oncology*Biology*Physics 2014;89(4):846–53.
34. Liu W, Zhu X, Li X, Li Y, Zhang X, Frank S, et al. SU-E-T-624: Comparison of PTV+PRV-Based Optimization and Robust Optimization in Intensity-Modulated Proton Therapy. Med Phys 2012;39(6Part20):3849–50.
35. McDonald MW, Liu Y, Moore MG, Johnstone PAS. Acute toxicity in comprehensive head and neck radiation for nasopharynx and paranasal sinus cancers: cohort comparison of 3D conformal proton therapy and intensity modulated radiation therapy. Radiation Oncology 2016;11(1):32.
36. Zenda S, Akimoto T, Mizumoto M, Hayashi R, Arahira S, Okumura T, et al. Phase II study of proton beam therapy as a nonsurgical approach for mucosal melanoma of the nasal cavity or para-nasal sinuses. Radiotherapy and Oncology 2016;118(2):267–71.
37. Romesser PB, Cahlon O, Scher ED, Hug EB, Sine K, DeSelm C, et al. Proton Beam Reirradiation for Recurrent Head and Neck Cancer: Multi-institutional Report on Feasibility and Early Outcomes. International Journal of Radiation Oncology*Biology*Physics 2016;95(1):386–95.
38. Phan J, Sio TT, Nguyen TP, Takiar V, Gunn GB, Garden AS, et al. Reirradiation of Head and Neck Cancers With Proton Therapy: Outcomes and Analyses. International Journal of Radiation Oncology*Biology*Physics 2016;96(1):30–41.
39. Chan S, Gerson B, Subramaniam S. The role of copper, molybdenum, selenium, and zinc in nutrition and health. Clin Lab Med 1998;18(4):673–85.
40. McDonald MW, Zolali-Meybodi O, Lehnert SJ, Estabrook NC, Liu Y, Cohen-Gadol AA, et al. Reirradiation of Recurrent and Second Primary Head and Neck Cancer With Proton Therapy. International Journal of Radiation Oncology*Biology*Physics 2016;96(4):808–19.
41. Holliday EB, Frank SJ. Proton Radiation Therapy for Head and Neck Cancer: A Review of the Clinical Experience to Date. International Journal of Radiation Oncology*Biology*Physics 2014;89(2):292–302.
42. Kooy HM, Grassberger C. Intensity modulated proton therapy. Br J Radiol 2015;88(1051):20150195.
43. Kooy HM, Grassberger C. Intensity modulated proton therapy. Br J Radiol 2015;88(1051):20150195.
44. Ding X, Li X, Qin A, Zhou J, Yan D, Chen P, et al. Redefine the role of range shifter in treating bilateral head and neck cancer in the era of Intensity Modulated Proton Therapy. J Appl Clin Med Phys 2018;19(5):749–55.
45. Lomax A. Intensity modulation methods for proton radiotherapy. Phys Med Biol 1999;44(1):185–205.
46. Michiels S, Barragán AM, Souris K, Poels K, Crijns W, Lee JA, et al. Patient-specific bolus for range shifter air gap reduction in intensity-modulated proton therapy of head-and-neck cancer studied with Monte Carlo based plan optimization. Radiotherapy and Oncology 2018;128(1):161–6.
47. Yasui K, Toshito T, Omachi C, Hayashi K, Tanaka K, Asai K, et al. Evaluation of dosimetric advantages of using patient-specific aperture system with intensity-modulated proton therapy for the shallow depth tumor. J Appl Clin Med Phys 2018;19(1):132–7.

48. Kraan AC, van de Water S, Teguh DN, Al-Mamgani A, Madden T, Kooy HM, et al. Dose Uncertainties in IMPT for Oropharyngeal Cancer in the Presence of Anatomical, Range, and Setup Errors. International Journal of Radiation Oncology*Biology*Physics 2013;87(5):888–96.
49. Liu W, Zhang X, Li Y, Mohan R. Robust optimization of intensity modulated proton therapy. Med Phys 2012;39(2):1079–91.
50. Müller BS, Duma MN, Kampfer S, Nill S, Oelfke U, Geinitz H, et al. Impact of interfractional changes in head and neck cancer patients on the delivered dose in intensity modulated radiotherapy with protons and photons. Physica Medica 2015;31(3):266–72.
51. Stuschke M, Kaiser A, Jawad JA, Pöttgen C, Levegrün S, Farr J. Multi-scenario based robust intensity-modulated proton therapy (IMPT) plans can account for set-up errors more effectively in terms of normal tissue sparing than planning target volume (PTV) based intensity-modulated photon plans in the head and neck region. Radiation Oncology 2013;8(1):145.
52. Liu W, Frank SJ, Li X, Li Y, Zhu RonX, Mohan R. PTV-based IMPT optimization incorporating planning risk volumes vs robust optimization. Med Phys 2013;40(2):021709.
53. Giantsoudi D, Grassberger C, Craft D, Niemierko A, Trofimov A, Paganetti H. Linear Energy Transfer-Guided Optimization in Intensity Modulated Proton Therapy: Feasibility Study and Clinical Potential. International Journal of Radiation Oncology*Biology*Physics 2013;87(1):216–22.
54. Hong L, Goitein M, Bucciolini M, Comiskey R, Gottschalk B, Rosenthal S, et al. A pencil beam algorithm for proton dose calculations. Phys Med Biol 1996;41(8):1305–30.
55. Kang JH, Wilkens JJ, Oelfke U. Non-uniform depth scanning for proton therapy systems employing active energy variation. Phys Med Biol 2008;53(9):N149–55.
56. Gu W, O'Connor D, Nguyen D, Yu VY, Ruan D, Dong L, et al. Integrated beam orientation and scanning-spot optimization in intensity-modulated proton therapy for brain and unilateral head and neck tumors. Med Phys 2018;45(4):1338–50.
57. Mohan R, Das IJ, Ling CC. Empowering Intensity Modulated Proton Therapy Through Physics and Technology: An Overview. International Journal of Radiation Oncology*Biology*Physics 2017;99(2):304–16.
58. Toramatsu C, Inaniwa T. Beam angle selection incorporation of anatomical heterogeneities for pencil beam scanning charged-particle therapy. Phys Med Biol 2016;61(24):8664–75.
59. Zhu X, Li Y, Mackin D, Li H, Poenisch F, Lee A, et al. Towards Effective and Efficient Patient-Specific Quality Assurance for Spot Scanning Proton Therapy. Cancers (Basel) 2015;7(2):631–47.