THE INFLUENCE OF NEW IRRADIATION TECHNIQUES OF PAROTID TUMORS FOR ORAL REHABILITATION

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ABSTRACT

Most salivary gland tumors arise in the parotid glands, but tumors of the submandibular or other minor salivary glands can also occur. Most tumors are treated with surgery, followed by postoperative radiotherapy when risk of local recurrence is high. Retrospective series suggest the addition of radiotherapy can reduce local recurrence rates from 30 per cent to 10 per cent but there is no effect on overall survival. Radiotherapy treatment can only produce good effects if it is delivered in an appropriate clinical context. Modern radiotherapy planning requires a comprehensive knowledge of cross sectional anatomy and the ability to visualize structures in three dimensions. IMRT is a new technology in radiation oncology that delivers radiation more precisely to the tumor while relatively sparing the surrounding normal tissues.

Key words: parotid tumour, radiotherapy, oral rehabilitation

INTRODUCTION

Most salivary gland tumors arise in the parotid glands and it presents as main therapeutic method surgical intervention followed by radiation in cases of local unfavorable prognosis [1]. Various retrospective studies have been demonstrated that adjuvant postoperative radiation purpose can reduce the risk of loco-regional recurrences over 30% at 10%, but failed to improve overall survival [2]. Postoperative radiotherapy is recommended in stages T_3-T_4, in incomplete resections with positive margins or perineural invasion bone, in forms with increased aggression or recurrences [3]. In such situations adjuvant chemotherapy appears to be effective. In advanced, inoperable, or loco-regional recurrences, local irradiation with heavy particles (neutrons or carbon ions) appears to have superior effects in terms of local control compared with standard photon radiation with no data concerning improvement of overall survival [4].

Adjuvant radiotherapy to the tumor bed is recommended for all forms of aggressive/intermediate salivary tumors – high grade mucoepidermoid, high grade adenocarcinoma and carcinoma arising from pleomorphic adenoma - except stages T_1 completely excised with clear margins. Ipsilateral lymphatic levels Ib, II and III must be irradiated prophylactic because of high risk of occult metastases, except when lymph node dissections were performed selective. Adjuvant radiation therapy is indicated for stages N_2/N_3 or in the presence of extracapsular spread.

In low grade tumors – mucoepidermoid carcinoma, low grade adenocarcinoma and acinic cell carcinoma - adjuvant irradiation is recommended where excision margins are positive or close (< 5 mm) generally after a preliminary discussion with surgeon and pathologist. Special attention must have for deep excision margin close to the facial nerve. In case of occult metastases N0 risk is lower than in aggressive forms, so prophylactic irradiation is not recommended.

Adenoid cystic carcinomas have a relatively high risk of locoregional recurrence and a propensity of perineural spread, therefore adjuvant radiation therapy is recommended for all forms (except the few stages T1 without perineural invasion).

Pleomorphic adenomas, although benign, are difficult to control only through surgery so radiotherapy is indicated in cases of excision with positive margins or outdated surgical cases (invasive tumors along the facial nerve). Prophylactic radiotherapy should be considered to prevent further recurrences in patients who have had a pleomorphic adenoma excised on more than one occasion previously, particularly if there is a short interval between recurrences relative to the life expectancy patient, or if further compromise cosmesis or function [5].

SEQUENCES AND MULTIMODAL TREATMENT STEPS

Adjuvant radiation therapy should be initiated ideally 4-6 weeks after surgical act. There is still no clear evidence about the role of concomitant chemotherapy.

Clinical examination can reveal invasion of local structures such as skin, facial nerve (palsy), or pterygoid muscles (lockjaw) or spread to draining lymph nodes. Fine needle biopsy guided by ultrasound can confirm the presence or malignancy.

Modern radiotherapy planning requires a comprehensive knowledge of cross sectional anatomy and the ability to visualize structures in three dimensions. Formal teaching in anatomy should be part of training, using standard atlases, various online resources, three-dimensional (3D) images, which have become more accessible with picture archiving and conservation systems (PACS). Cross-sectional imaging is performed to assess tumor extension (particularly with deep edges positioned opposite to the parapharyngeal spaces) and to asses local lymph nodes.

CT scanning provides detailed cross-sectional anatomy of the normal organs, as well as 3D tumor information. These images provide density data for radiation dose calculations by conversion of CT Hounsfield units into relative electron densities using calibration curves. Compton scattering is the main process of tissue interaction for megavoltage beams and is directly proportional to electron density. Hence CT provides ideal density information for dose corrections for tissue inhomogeneity, such as occurs in lung tissue. Clinical studies have shown that 30–80 per cent of patients undergoing radiotherapy benefit from the increased accuracy of target volume delineation with CT scanning compared with conventional simulation.

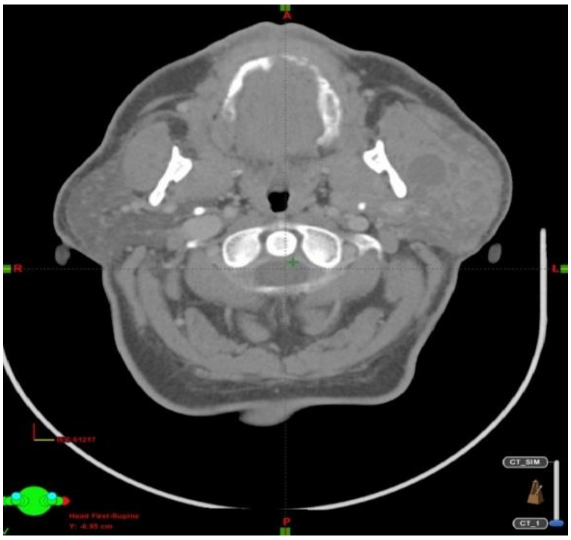

Figure 1. CT scan for a left parotid tumor

MRI examination is preferred to CT because examinations may indicate a greater accuracy of perineural invasion. The scan volume starts from skull base and include all viscerocranium and cervical lymph areas. Preoperative scanning is compulsory and improve prognosis for defining volumes irradiated in postoperative radiotherapy.

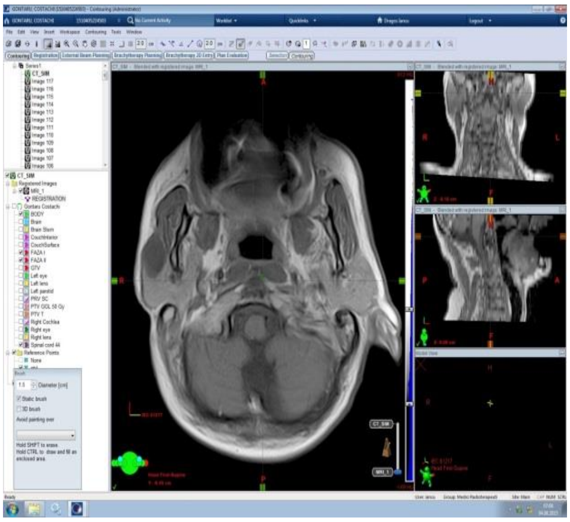

Figure 2. MRI scans of left parotid tumor before excision

CT images fused with preoperative MRI are carefully evaluated to detect lymph nodes or macroscopic residual outstanding. The volume of irradiation is determined by pathological features such as perineural invasion of a major nerve, and eventually after discussions with surgeon and pathologist. The delineation of the clinical target volume will be individualized based on the extent of the disease and surgery. Considering that irradiation is adjuvant to surgery, the GTV cannot be limited even in the presence of residual masses.

Gross tumor volume (GTV) is the primary tumor or other tumor mass shown by clinical examination, at examination under anesthetic (EUA) or by imaging. GTV is classified by staging systems such as TNM (UICC), AJCC or FIGO. Tumor size, site and shape may appear to vary depending on the imaging technique used and an optimal imaging method for each particular tumor site must therefore also be specified. A GTV may consist of primary tumor (GTV-T) and/or metastatic lymphadenopathy (GTV-N) or distant metastases (GTV-M). GTV always contains the highest tumor cell density and is absent after complete surgical resection.

Clinical target volume (CTV) contains the GTV when present and/or subclinical microscopic disease that has to be eradicated to cure the tumor. CTV definition is based on histological examination of post mortem or surgical specimens assessing extent of tumor cell spread around the gross GTV, as described by Holland *et al.* (1985) for breast cancer. The GTV-CTV margin is also derived from biological characteristics of the tumor, local recurrence patterns and experience of the radiation oncologist. A CTV containing a primary tumor may lie in continuity with a nodal GTV/CTV to create a CTV-TN (e.g. tonsillar tumor and ipsilateral cervical nodes).

Planning target volume (PTV) is used in treatment planning to select appropriate beams to ensure that the prescribed dose is actually delivered to the CTV. [6].

CTV60 is made based on loco-regional extension and on the surgical act. Particular attention is given to the deep excision margin which is likely to be close or involved if the facial nerve has been preserved. Para-pharyngeal and infra-temporal fossa spaces must be covered adequately. In general CTV60 medial limit must be tangent to the side of the internal jugular vein, but when the tumor affects the deep lobe of parotid irradiation volume should include the para-pharyngeal space. CTV60 lateral limit must be just under the skin, without inclusion of postoperative scar. The position of contralateral parotid on the planning CT can be useful guide to the superior and inferior limit of the CTV60. In adenoid cystic carcinomas, the CTV60 must include the entire path of the facial nerve starting from stylo-mastoidian foramen at the skull base. Primary irradiation volume must include ipsilateral infradigastric lymph nodes because inferior pole of the parotid reach on this region. [6].

If there are indications of adjuvant radiation after neck dissection, cervical lymph levels I- V levels must be included in CTV60 volume. There is still no concrete data about bilateral elective neck irradiation. The recommended dose in such cases of positive lymph nodes is 60 Gy/30 fractions. If prophylactic irradiation areas include nodal irradiation volumes Ib, II and III, an intermediate CTV44 volume can be defined.

As organs at risk (OAR), besides classical (spinal cord, brainstem, lens, optic nerves) should be outlined contralateral parotid, internal ear and cochlea. The contralateral parotid does not receive a higher dose as 28Gy (more than xerostomia occurs). The inner ear should be defined as an OAR, as reducing dose to the cochlea may reduce the risk of deafness.

Similar principles can be applied for volume definition for tumors of the submandibular or minor salivary glands. In adenoid cystic carcinomas the nerve innervating the primary tumor site should be include up to the skull base. In adenoid cystic carcinomas of the submandibular gland this should include the lingual nerve (a branch of the mandibular nerve, V_3) back to the *foramen ovale* and the marginal mandibular branch of the facial nerve to the stylomastoid foramen. For tumors arising in or close to the midline (e.g. hard palate), prophylactic lymph node volumes should be outlined bilaterally if lymph nodes are to be included in the CTV.

Parotid gland irradiation depends on the available equipment, staff training and the possibility of initiating therapy in an optimal range. In principle there are using ^{60}Co machines, linear accelerators and neutron therapy and as basic therapy there are three approaches using conventional, 3D conformational irradiation (3D-CRT), and intensity modulated radiation therapy (IMRT) planning.

Conventional therapy uses 2-3 oblique photons beams and is available on older ^{60}Co machines and linear accelerators (energies of 4 or 6MV). In principle, this technique can provide the uniformity of the dose distribution on the CTV without increasing dose to the adjacent critical organs.

For this purpose there are involves unilateral anterior and posterior wedged pair fields. A slight inferior angulation of the beams avoids an exit dose through the contralateral eye. An additional third lateral photon beam may provide a more homogenous distribution but will increase dose to the contralateral parotid gland and possibly to the spinal cord.

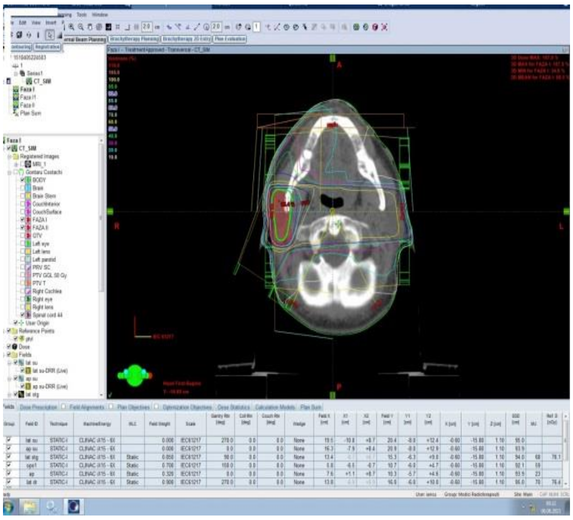

Figure 3. Conformal 3D doze solution for left parotid tumor. (Noted incomplete distribution of 95 isodose around parotid volume)

3D conformational radiotherapy (3D-CRT) use conformal geometrically shaped beams of uniform intensity. It provides superior coverage and enhanced protection of organs at risk and more normal tissues may be spared with technique [7]. Hotspots in the mandible of > 107% should be avoided in order to reduce the risk of osteoradionecrosis. Excessive dose in the temporo-mandibular joint should avoid reducing the risk of long-term temporo-mandibular joint dysfunction and lockjaw. The cochlear dose should be kept below 50 Gy if possible to minimize the risk of hearing damage.

Intensity modulated radiation therapy (IMRT) is a new technology in radiation oncology that delivers radiation more precisely to the tumor while relatively sparing the surrounding normal tissues. It also introduces new concepts of inverse planning and computer-controlled radiation deposition and normal tissue avoidance in contrast to the conventional trial-and-error approach. IMRT has wide application in most aspects of radiation oncology because of its ability to create multiple targets and multiple avoidance structures, to treat different targets simultaneously to different doses as well as to weight targets and avoidance structures according to their importance. By delivering radiation with greater precision, IMRT has been shown to minimize acute treatment-related morbidity, making dose escalation feasible which may ultimately improve local tumor control. IMRT has also introduced a new accelerated fractionation scheme known as SMART (simultaneous modulated accelerated radiation therapy) boost. By shortening the overall treatment time, SMART boost has the potential of improving tumor control in addition to offering patient convenience and cost savings. IMRT techniques employ variable intensity across multiple radiation beams leading to the construction of highly conformal dose distributions. This is achieved by subdividing each radiation beam into smaller radiation beam lets and varying the individual intensities of these beams lets. The advantages of this technique are improved target volume conformity, particularly in volumes with complex concave shapes, and improved sparing of normal tissues and organs at risk (OARs) resulting in reduced acute and late toxicities. IMRT also has the ability to produce inhomogeneous dose distributions, which allows the simultaneous delivery of different doses per fraction to separate areas within the target volume. This could facilitate localized dose escalation strategies without increasing total treatment time (for example, by using hypo-fractionated regimens), which may have the potential radiobiological benefit of reducing the impact of accelerated repopulation in tumors clonogens. Despite the obvious benefits of IMRT, there are still some disadvantages. The planning and quality assurance (QA) processes required for IMRT are more complex and time-consuming compared with conventional conformal radiotherapy (CRT) techniques, which can have significant impact on departmental resources. However, several commercial systems are now available that allow multiple plan measurement of IMRT plans and facilitate batching of patient QA measurements to improve efficiency. A standard IMRT plan often requires multiple fixed angle radiation beams, which can increase treatment delivery time. This can impact on patient comfort on the treatment couch, reproducibility of treatment position and intra-fraction motion. There are also some concerns that the increased treatment time could have radiobiological implications owing to the possibility of increased tumor cell repair and repopulation during the extra time required to deliver the treatment [8].

IMRT plans use a larger number of monitor units (MU) compared with conventional CRT plans leading to an increase in the amount of low dose radiation to the rest of the body.

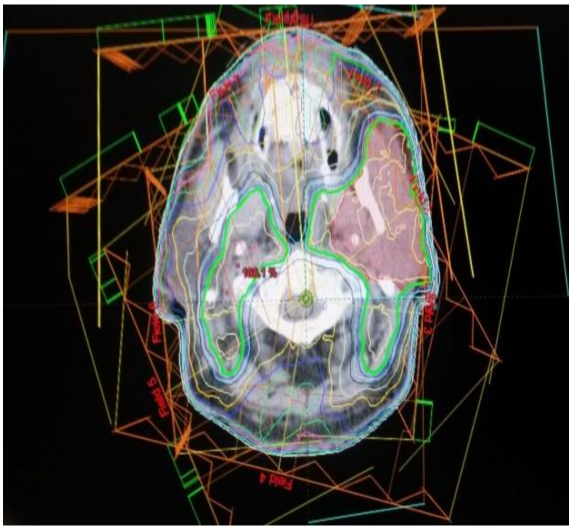

Figure 4. IMRT doze solution for left parotid tumor

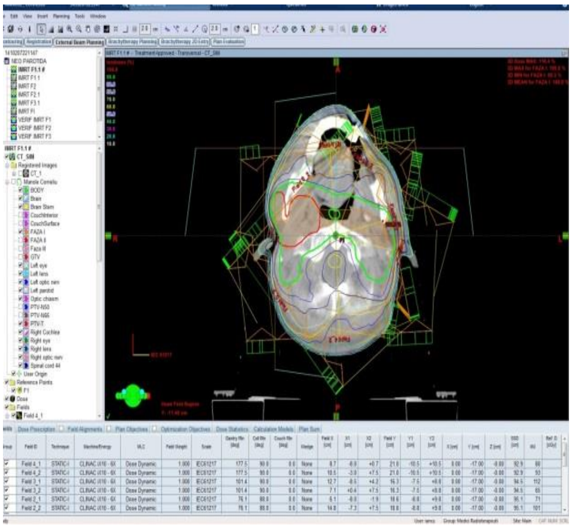

Figure 5. IMRT dose solutions for a right parotid tumor

The number of MU used in fixed field IMRT depends, to some degree, on the IMRT technique; usually more MU is required in the sliding window (SW) or dynamic IMRT technique. In this technique, each radiation beam is modulated by continuously moving multi leaf collimators (MLCs). This is in contrast to the step-and-shoot (SS) or static techniques in which each beam is subdivided into multiple segments with differing MLC shapes and the beam is switched off between segments. The increase in MU and subsequent increase in low dose radiation has led to concerns of increased risk of secondary radiation-induced malignancies, which is of particular relevance in pediatric patients or patients with long life expectancies. There are estimates in the literature that the number of MU in an IMRT plan is two to three times higher than a conventional radiotherapy plan with an increase in the incidence of radiation-induced secondary malignancies from 1−1.75% for patients who survive for 10 years or more.

More recently, there has been some interest in arc-based or rotational therapies in an attempt to overcome some of the limitations associated with fixed field IMRT.

The basic concept of arc therapy is the delivery of radiation from a continuous rotation of the radiation source and allows the patient to be treated from a full 360° beam angle. Arc therapies have the ability to achieve highly conformal dose distributions and are essentially an alternative form of IMRT.

However, a major advantage over fixed gantry IMRT is the improvement in treatment delivery efficiency as a result of the reduction in treatment delivery time and the reduction in MU us age with subsequent reduction of integral radiation dose to the rest of the body. In addition to the subsequent advantages from the shorter treatment delivery time, a further potential benefit is the availability of extra time within a set treatment appointment time slot to employ image-guided radiotherapy (IGRT).

IGRT involves the incorporation of imaging before and/or during treatment to enable more precise verification of treatment delivery and allow for adaptive strategies to improve the accuracy of treatment. The main drawback of IGRT is the requirement for more time on the treatment couch and an increase in the total amount of radiation to the patient, especially with daily IGRT imaging schedules. These disadvantages are less of an issue with arc therapies, which have shorter treatment delivery times and fewer MU.

There are inherent limitations with these planning studies. Even if the same strict planning objectives and calculation algorithms were used, it is extremely difficult to completely eliminate planner bias especially if multiple planners are involved in the process. Direct comparisons between different studies are not possible because of significant differences in target volume definitions, dose prescription and treatment schedules. Radiation techniques also vary between the studies, for example in the number of fields and arcs used in the fixed field IMRT and VMAT plans, and IMRT technique (SW or SS). As a result, it is not surprising that the results on PTV coverage and OAR sparing can appear conflicting between the studies.

Neutron therapy when they can be accessed is the first choice for inoperable tumors, residual masses or major relapses. Various studies have shown a higher local control rate risk however of a higher toxicity [5]. A study from Heidelberg for advanced, inoperable, recurrent, or incompletely resected adenoid cystic carcinoma compared results of treatment with neutrons, photons, or mixed beam. Sever grade (3 and 4) toxicity was 19% with neutrons, compared to 10% with mixed beam and 4% with photon therapy. The 5-yaer local control was 75% for neutrons and 32% for mixed beams and photons survival was identical. [5].

CONCLUSIONS

1. IMRT planning studies have reported reduced dose to the cochlea. An equispaced nine-beam coplanar technique has been described, but this risks increasing dose to the contralateral parotid. An ipsilateral four-beam IMRT planning solution has also been used but may not be better than a 3D-conformal beam arrangement.

2. IMRT has the potential to deliver the most conformal radiotherapy to complex target volumes with greater sparing of normal tissues. There are relatively few instances in oral cavity tumors where this is likely to give a therapeutic advantage as PTVs are usually convex and as the contralateral parotid can already be spared if the treated volume is unilateral. Moreover, the extra dose to the oral mucosa and contralateral mandible from IMRT may increase acute and late effects. IMRT may offer an advantage when both sides of the neck are included in the PTV, both to spare one parotid gland and reduce the risk of xerostomia, and to avoid the uncertainties inherent in a plan with matched posterior electron and anterior neck photon fields. Beam arrangements similar to those chosen for oropharynx IMRT are used.

3. The amount of oral cavity and oropharynx included in the treatment volume may predict the degree of swallowing problems seen during treatment. Treatment of mucositis should be given within a multidisciplinary team, which reviews the patient weekly. Advice on jaw exercises can reduce the risk of lockjaw and TMJ dysfunction [10].

4. Conductive hearing loss due to middle ear effusions can occur during radiotherapy and take several months to improve after treatment has finished. If subjective hearing loss persists two months after treatment, an audiogram should be performed. If there is evidence of conductive hearing loss, a grommet may be indicated [11].

REFERENCES

1. Ang KK, Kaanders Jham, IJ Peters. Radiotherapy for Head and Neck Cancers: Indications and techniques. Philadelphia: Lea & Febiger; 1994: 109-118.
2. Garden AS, el-Naggar AK, Morrison WH et al. Postoperative radiotherapy for malignant parotid gland Tumors of. Int J Radiat Oncol Biol Phys 1997; 79-85.
3. Kirkbride P, Liu FF, O'Sullivan B et al. Outcome of curative management of malignant parotid gland Tumors of. J.Otolaryngol 2001; 30: 271-279.
4. Douglas JG Koh W, Austin-Seymour M et al. Treatment of salivary gland cancer with fast neutron radiotherapy. Head Neck Surg Arch Otolaryngol. 2003; 129: 944-948.
5. Chen AM, Garcia J, NY Lee et al. Patterns of nodal relapse after surgery and postoperative radiation therapy for carcinomas of the major salivary glands and minor: what is the role of the elective neck irradiation? Int J Oncol Biol Phys radiated, 2007, 67: 988-94.
6. Barrett Ann, Dobbs Jane, Morris S, Roques T - Practical Radiotherapy Planning 4Th Ed 2009: 184.
7. Nutting CM, Rowbottom LP, Cosgrove VP et al. Optimization of radiotherapy for carcinoma of the parotid gland: A comparision of conventional 3D conformal, IMRT and techniques. Radiother Oncol 2001; 60: 163-172.
8. Bragg CM, Conway J, Robinson MH. The intensity-modulated radiotherapy rolls of in the treatment of parotid Tumors. Int J Radiat Oncol Biol Phys 2002; 52: 729-738.
9. Huber PE, Debus J, Latz D et al. Adenoid cystic carcinoma radiotherapy for advanced: neutrons, photons or mixed beam? Radiother Oncol 2001; 59: 161-167.
10. Jerenczek-Fossa BA, Zarowski A, Milani F et al. Treatment Complications induced. Radiotherapy-induced ear toxicity. Cancers Treatment Reviews 2003; 29: 417-430.
11. JR Simson, Thawley SE, Matsubase HM. Adenoid cystic carcinoma of salivary gland: Treatment with irradiation and surgery. Radiology 1984; 151: 509.