Oral Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Salivary Gland. Photon beam and particle radiotherapy: Present and future

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ARTICLE INFO

Article history:
Received 10 February 2016
Received in revised form 20 June 2016
Accepted 27 June 2016
Available online xxxx

Keywords:
Malignant salivary gland cancers
Intensity modulated radiation therapy
Proton therapy
Carbon ion therapy
Particle beam therapy
Adenoid cystic carcinoma
Postoperative radiotherapy
Definitive radiotherapy

ABSTRACT

Salivary gland cancers (SGCs) are rare diseases and their treatment depends upon histology, stage and site of origin. Radical surgery is the mainstay of treatment but radiotherapy (RT) plays a key role in both the postoperative and the inoperable setting, as well as in recurrent disease. In the absence of prospective randomized trials, a wide retrospective literature suggests postoperative RT (PORT) in patients with high risk pathological features.

SGCs, and adenoid cystic carcinoma (ACC) in particular, are known to be radio-resistant tumors and should therefore respond well to particle beam therapy. Recently, excellent outcome has been reported with radical carbon ion RT (CIRT) in particular for ACC. Both modern photon- and hadron-based treatments are effective and are characterized by a favourable toxicity profile. But it is not clear whether one modality is superior to the other for disease control, due to the differences in patients' selection, techniques, fractionation schedules and outcome measurements among clinical experiences.

In this paper, we review the role of photon and particle RT for malignant SGCs, discussing the difference between modalities in terms of biological and technical characteristics. RT dose and target volumes for different histologies (ACC versus non-ACC) have also been taken into consideration.

Introduction

Salivary gland cancers (SGCs) are uncommon diseases accounting for only 2–6.5% of all head and neck cancers, and are characterized by considerable variability in their biology and natural history [1]. Mucoepidermoid carcinoma (MEC), adenoid cystic carcinoma (ACC), and adenocarcinoma are the most frequent diagnoses, representing >75% of all SGCs, although their frequency varies according to the site of origin (major vs minor salivary glands) [2]. Prognosis among SGCs differs according to histology and grading: non-ACC and high-grade tumors are associated with a poorer prognosis compared with low-grade tumors [3–5].

Treatment of SGCs depend upon histology, involved gland and location within the gland. In addition, some gene translocations and rearrangements correlating with specific SGTs seem associated not only with clinical and pathological parameters but also with improved prognosis becoming attractive targets for future, therapeutic possibilities [6].

While these intriguing treatments remain eagerly awaited, complete surgical resection, with adequate free margins, is the mainstay of treatment for resectable cases. Small, well-localized, low-grade tumors excised with clear margins are best treated with surgery alone [2]. Postoperative radiotherapy (PORT) is recommended in high-risk patients when adverse prognostic factors based on pathology (T size, lymph node involvement, close/positive margins, vascular/perineural invasion and high grade) can be identified [2]. Unresectable or inoperable SGCs can be managed with RT alone, even though curative purposes are hardly achievable [2].

Overall, SGCs represent a major challenge for the Radiation Oncologists' community not only for their historically known radio-resistance, but also given its frequently horseshoe-shaped target volume (e.g. in case of perineural invasion) and their proximity to radiosensitive normal structures (e.g. tumors arising from minor salivary glands in paranasal sinuses).

Several methods of RT delivery have been investigated in order to improve tumor control rates while reducing toxicity. As modern photon RT techniques may also permit the safe delivery of higher doses, SGCs treatments are evolving toward wider use of sophisticated photon radiation techniques including Intensity Modulated

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http://dx.doi.org/10.1016/j.oraloncology.2016.06.019
1368-8375/

Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT). These techniques allow to optimize the dose delivery to complex target volumes, including tumors of the head and neck district, while limiting doses to organs at risk. On the other hand, multiple fields arrangements - or gantry rotation they are based on - leads to an increase of the body area receiving small doses [7].

Some limitations of conventional RT can be substantially overcome by using hadrons. Hadrons are subatomic particles subject to a strong nuclear force, and they can be used in a therapy called hadron therapy or particle beam RT. This includes all forms of treatment that use beams of hadrons, i.e. beams of particles made up of quarks such as neutrons, protons and ions [8].

At present, the most used types of hadron therapy are proton therapy (PT) and carbon ion radiotherapy (CIRT). The number of particle RT facilities, in particular centers equipped with protons and carbon ions, is rapidly increasing. For example, considering facilities capable of treating deep seated tumor and excluding those focused only on eye treatment, the number of operating proton centers in the United States has increased from 3 to 18 in the past decade [9], with 11 more being under construction [10]. In Europe, the interest in hadron therapy has been growing rapidly over the last 5 years. Historically, two facilities have been treating patients with deep seated tumors with protons for more than 20 years, Villingen-PSI, Switzerland, and the Orsay Center, France [11,12]. In the last 5 years nine more facilities have become operational in Europe [9]; three of them (HIT in Heidelberg, CNAO in Pavia and MIT in Marburg) are dual facilities with both protons and carbon ions [13,14]. Seven more facilities are under construction in Europe (1 dual facility and 6 proton facilities) and seven more are in planning stage. Interest in particle beam RT has been burgeoning among oncologists and their use for treatment of SGTs is increasing mostly because of their biological and physical advantages compared with photon RT. However, due to the high cost of particle therapy and the very low number of equipped facilities, careful patient selection remains absolutely critical.

Both modern photon- and hadron-based treatments have been shown to be effective and are characterized by a favorable toxicity profile [15]. However, it remains unclear whether one modality is superior over the other in terms of local control due to the differences in selected patients, techniques and outcome measurements among clinical series and the absence of prospective randomized trials.

This paper discusses the different biological and technical characteristics of photon and particle beam RT and their impact on SGCs, and reviews the role of RT for malignant SGCs with both technical modalities, with a focus on RT dose and target volumes for different histologies (ACC versus non-ACC). Moreover, we discuss about the use of systemic therapy and the potential impact of genetic alterations and biomarkers in specific SGCs while planning RT

Radiobiological aspects

Hadrons and photons differ in their radiobiological characteristics because of the different relative biological effect on tumor and normal tissues. Relative biological effectiveness (RBE) is defined as the ratio between the dose of the reference photon radiation required to produce a given reaction and the dose of a particle beam necessary to have the same effect (e.g. skin and mucosal reactions). A smaller physical dose of hadrons, as compared with megavoltage photons, is needed to produce a similar reaction [16,17]. For hadron therapy, the dose was previously expressed as photon equivalent dose, i.e. Gray equivalent (GyE), calculated by multiplying the particle beam physical dose by the RBE value; the correct notation currently used is Gy [RBE]. With increasing atomic mass and ion electronic charge, ionization density and Linear Energy Transfer (LET) increases. Biological efficacy is related to LET in a complex non-linear way, the key parameter being DNA diameter. Damage produced by a radiation becomes very difficult to repair when the mean distance between two ionizations is comparable with DNA diameter. In this situation, a single particle can produce clustered damage in a region of a few base pairs that is almost irreparable. Photons are low LET particles. They cause sparse ionization that result in DNA damage that can be repaired by the normal repair mechanisms. At first approximation, also protons can be described as low LET particles [18].

Fast neutrons are high LET particles. They cause dense ionization that results in almost irreparable direct damage to DNA. Their efficacy depends only weakly on cell cycle, efficiency of repair mechanisms, oxygenation, and viability of apoptotic pathways [19]. High-LET carbon ion beams, characterized by RBE $\approx$3, may cause DNA damage clusters that are no longer repairable (this phenomenon is more evident in tumor than in normal cells) [20,21]. Moreover, they display low oxygen enhancement ratio (OER) and reduced variation of sensitivity around the cell cycle [10]. According to Fokas et al., high LET radiation should be selectively used for radiobiological reasons in tissues that are slowly proliferating, later responding, have a high capability for sub-lethal damage repair, and in those histologies which have been shown to be highly resistant to conventional treatment [22].

Physical aspects

Charged particles and photons differ also in terms of their physical properties. This difference lies in the energy loss mechanism. In the clinically-useful energy range, photons exhibit an initial rise (build-up) of the dose distribution up to a maximum, followed by an exponential absorption with increasing tissue depth. On the contrary, charged particles deposit a small amount of energy at body surface and slow down progressively losing energy. As particle energy reduces, the interactions with tissue electrons increase along with the amount of energy loss, leading to a maximum just before particles come to rest in tissue. The result is a steep increase of dose deposition, i.e. the Bragg peak, near the end of the range and a sharp drop of the dose after the Bragg peak [23,24].

The characteristic is common to protons and heavier ions. For the latter, however, there is still a minor dose contribution beyond the peak, due to lighter fragments produced in nuclear reactions with the tissue [25]. Compared with protons, the ratio of Bragg peak dose versus dose in the entrance region is larger for heavy ions, i.e. carbon ions, while angular and energy straggling are negligible due to their larger mass [26].

The in-depth dose distribution of charged particles allows a more accurate dose deposition, resulting in an increased therapeutic ratio. The high-dose area could be better confined to the tumor volume and the irradiation of the surrounding normal tissue minimized, thus resulting in a better sparing of organs at risk close to the target compared with photons [27]. Physical properties of photons and neutrons are less favorable and there is an exponential decrease in the dose deposited along penetration depth. The radiobiological properties of neutrons remain constant during their path; therefore besides high tumor control they can produce irreparable damage on healthy tissues and severe clinical toxicity [28]. The radiobiological properties of carbon ions are not constant because their LET increases along the penetration path; therefore the entrance channel receives low dose with low LET while the last part of the path (where the Bragg peak is) receives high dose with high LET, and consequently high RBE, that is confined to the target.

Please cite this article in press as: Orlandi E et al. Salivary Gland. Photon beam and particle radiotherapy: Present and future. Oral Oncol (2016), http://dx.doi.org/10.1016/j.oraloncology.2016.06.019