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Review

Intensity modulated radiation therapy in nasopharyngeal carcinoma

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ABSTRACT

Radiation therapy (with associated chemotherapy) is the standard treatment for nasopharyngeal carcinoma. Conformal intensity-modulated radiation therapy is a new and particularly interesting technique for these tumors, due to their complex volumes close to many critical organs. Better dosimetric results and improved protection of adjacent healthy tissue have been shown compared with conventional 2D or 3D radiation therapy, with significantly reduced side-effects, notably xerostomia. Excellent local control rates have been reported.

1. Introduction

Nasopharyngeal carcinoma, especially when of the undifferentiated type, differs from other head and neck cancers geographically and ethnically and by its association with Epstein-Barr virus and specific treatment requirements. Treatment is hindered by the anatomic proximity of numerous critical organs, restricting indications for surgery to biopsy for initial histologic diagnosis and to cases of relapse. Radiation therapy (RT) is the keystone of local treatment [1].

In locally advanced cancer, the overall survival benefit of associating radiation therapy and chemotherapy was demonstrated in Baujat et al.'s meta-analysis, especially when the association was concomitant [2].

The efficacy of adjuvant chemotherapy is under assessment, certain retrospective reports suggesting an impact on tumor control [3].

Progress in imaging (magnetic resonance imaging (MRI) and positron emission tomography coupled to computed tomography (PET-CT)) has improved initial extension assessment in nasopharyngeal carcinoma [4], enhancing the precision of RT planning.

More recently, conformal intensity-modulated radiation therapy (IMRT) has become standard clinical practice.

IMRT uses multiple small radiation beams of varying intensities and shapes thanks to a multileaf collimator.

This optimizes tumor area coverage while protecting healthy neighboring organs.

The present study successively examines the various radiation target volumes and healthy organs to be spared (organs at-risk: OARs) and the fractionation and dose options. We shall also review the data demonstrating the specific benefit of IMRT over 2D and 3D strategies. Finally, we shall report results for local control, and look at foreseeable future developments.

2. Definition of target volumes

RT planning requires target volumes to be defined on a CT-scan for dosimetry. This is performed in dorsal decubitus, with a 5-point thermoformed contention mask (immobilization of head, neck and shoulders), without and, if possible, with intravenous iodized contrast injection, and thin (3 mm) slice acquisition from vertex to superior mediastinum. The target volumes to be defined are as follows [5].

2.1. GTV

Gross tumor volume (GTV) is the tumor mass visible on clinical examination, endoscopy and imaging. It includes the nasopharyngeal tumor (tumoral GTV) and involved lymph nodes (nodal GTV). GTV after neoadjuvant chemotherapy includes not only the residual volume but the whole initial tumor and involved lymph nodes. Delineation is improved by fusion of the planning CT scan and the initial MRI. However attractive the option may seem, fusion with PET-CT is not recommended in routine practice, for lack of validation in the literature.

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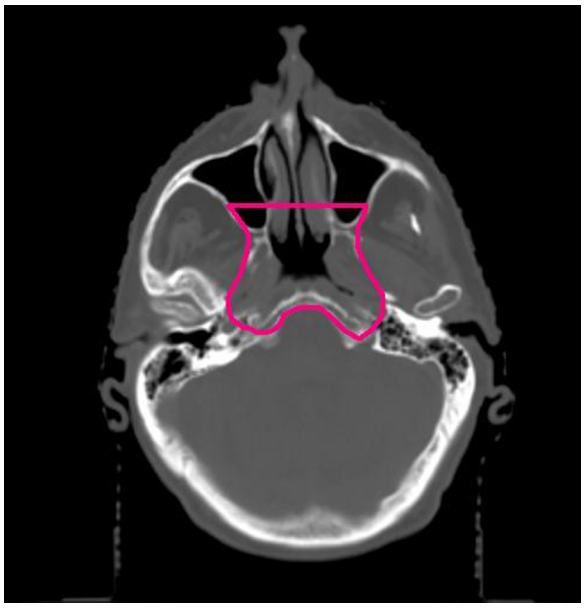

Fig. 1. Example of CTV definition including nasopharynx, posterior third of nasal cavities and maxillary sinuses (anteriorly), parapharyngeal space (laterally) and clivus and retropharyngeal space (posteriorly).

2.2. CTV

Clinical target volume (CTV) includes GTV plus any immediately neighboring microscopic tumor or lymph-node extensions, taking account of the natural extension pathways of nasopharyngeal carcinoma. CTV thus includes:

- above: the inferior part of the sphenoid sinus, and the middle cranial fossa, including foramina (ovale and lacerum);
- below, the oropharyngeal mucosa;
- laterally, the parapharyngeal spaces;
- anteriorly, the posterior part of the nasal cavities and the pterygomaxillary fossa;
- posteriorly, the retropharyngeal space and clivus [1,6,7] (Figs. 1 and 2).

Some authors also include the cavernous sinus (superiorly), pterygoid muscles and carotid space (laterally) and the posterior third of the maxillary sinuses (anteriorly) in the CTV [7–9].

Nasopharyngeal carcinoma being highly lymphophilic, nodal CTV systematically includes bilateral levels II to V (Robbins classification) and the bilateral retropharyngeal lymph-node areas [10,11].

2.3. PTV

Planning target volume (PTV) is delineated geometrically by drawing a 3–5 mm margin around the tumoral or lymph-node CTV, to allow for uncertainty related to patient positioning and systematic or variable internal movement.

2.4. Organs at risk (OARs)

Healthy organs are also delineated, to ensure protection: brainstem, brain (temporal lobe and posterior fossa), spinal cord, optic chiasm, cochlea, optic nerves, lens, parotid glands, submandibular glands, mandible, temporomandibular joints, pharyngeal constrictor muscles, larynx, esophagus, and thyroid and pituitary glands.

3. IMRT dose prescription

IMRT uses 5 to 7 radiation beams, with fluence adjusted from fraction to fraction. Planning is inverse: i.e., dose ranges to be delivered to the PTV and OARs are determined initially by the physician, and dosimetry seeks to remain within these predefined limits. IMRT enables a tailored dose to be delivered within the volume to be treated, several CTVs and thus several distinct PTVs being defined. Dose per PTV is determined according to risk of invasion (Fig. 3) [12].

There are a number of IMRT techniques: SIB (Simultaneous Integrated Boost), SMART (Simultaneous Modulated Accelerated Radiation Therapy), or sequential (partially conformal 3D RT and partially IMRT). In SIB the highest dose per fraction is delivered to the highest-risk PTV, which usually includes the GTV, with lower doses to medium or low-risk PTVs. High-risk PTV dose per fraction is around 2 Gy/day. SMART combines integrated boost and accelerated radiation with a smaller number of fractions; high-risk PTV dose per fraction is thus greater than 2.2 Gy/day, and often around 2.3 Gy/fraction [12].

Table 1 shows examples of dose levels and fractionation in nasopharyngeal carcinoma IMRT [13–16].

4. Dose escalation

Retrospective studies of nasopharyngeal carcinoma indicate a tumoricidal dose of $\geq$ 70 Gy. Dose escalation has been described in nasopharyngeal carcinoma, by brachytherapy or conformal or stereotaxic radiation, but with increased late toxicity [17,18].

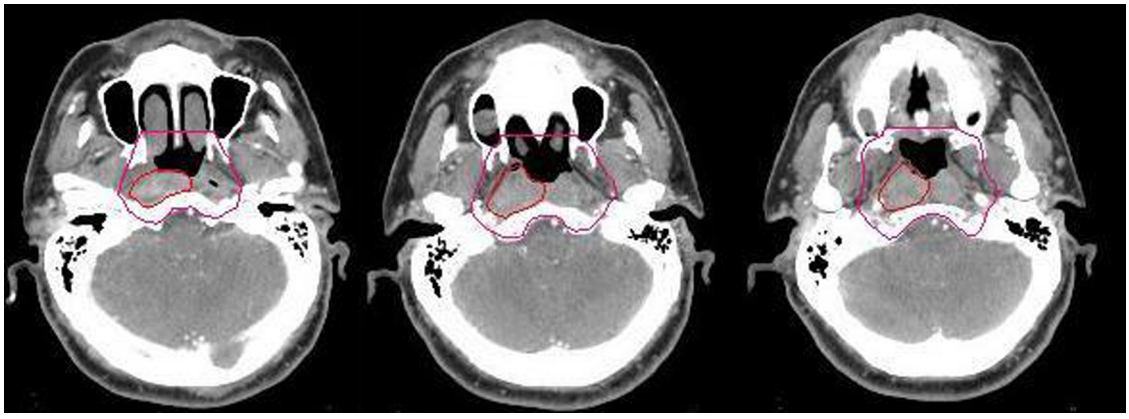

Fig. 2. Example of delineation with tumoral GTV (red) and tumoral CTV (pink).