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REVIEW ARTICLE

Conservation of salivary function and new external head and neck radiation techniques

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Xerostomia

Summary
Introduction: New radiation therapy techniques seek to adapt dose distribution to three-dimensional tumor geometry, so as to deliver the lowest possible dose to normal tissue and at-risk organs. This is expected to enhance locoregional control and survival and to reduce complications and thereby improve quality of life. Post-radiation xerostomia significantly deteriorates quality of life.
Material and methods: New external radiation techniques (such as intensity-modulated conformal radiation therapy, RapidArc VMAT arc therapy, tomotherapy, CyberKnife®, protontherapy, use of carbon ions) applicable in ENT are reviewed.
Results: Preliminary data show interesting results in terms of salivary function with highly conformal techniques.
Conclusion: In France, assessment is ongoing, financed under the Health Ministry's ''Support for Expensive Innovatory Techniques'' scheme (STIC [*Soutien aux techniques innovantes coûteuses*]), as routine use is growing rapidly.

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Introduction

New radiation therapy techniques seek to adapt dose distribution to three-dimensional tumor geometry, so as to deliver the lowest possible dose to normal tissue and at-risk organs. This is expected to enhance locoregional control and survival and to reduce complications and thereby improve quality of life.

Post-radiation xerostomia significantly deteriorates quality of life [1—4]. The parotid glands produce most of the stimulated salivary flow, but the other salivary glands, such as the oral cavity accessory glands, contribute to the production of non-stimulated saliva and conversely to the sensation of chronic dry mouth. Apart from the case of radiation treatment of salivary gland tumor and certain selected tumors (e.g., lateralized oropharynx T1 N0 tumor), where radiation may be unilateral, 2D radiation treatment of head and neck cancer (HNC) is bilateral, and involves the parotids. The dose delivered induces irreversible xerostomia.

One of the most important parameters in radiation planning (Fig. 1) is the critical dose delivered to healthy organs and the quality of contouring of organs receiving radiation. Conservation of healthy organs has to be weighed against oncological risk, which depends upon the initial cancer grade: 60—70% of HNCs are grades III—IV and 30—40% grades I—II. For locally advanced stages, current treatment standards recommend concomitant radiochemotherapy (isolated or postoperative), which improves overall survival and locoregional control, but also increases certain forms of late toxicity [5]. Certain medical treatments have been tested for salivary function conservation, but results with an association of cytoprotectant (amifostine, pilocarpine) and classic radiation therapy are contradictory and treatment is costly and sometimes poorly tolerated [6—11] with, in the case of pilocarpine, only transitory benefit.

The salivary glands are better visualized on MRI than on CT [12]. MRI may be associated to dosimetric scan. PET scan to determine target volumes is currently under study [13].

The sensitivity pattern of radiation varies with tissue architecture [14]. Architecture is said to be *in series* when organ function depends on each functional subunit: the organ is seen as a chain of connected links, a break in any one of which leads to loss of function. A typical example is bone-marrow: radiation myelopathy, while exceptional, may induce tetraplegia at an interval of between six months and several years. The parotid glands have an architecture *in parallel*, and come in pairs. It may be reasonable to sacrifice one parotid if conservation would incur a risk in terms of ipsilateral tumor or lymph-node volume, while at least partially conserving contralateral parotid volume. The data initially established for the parotids by Eisbruch were based on the ratio of stimulated to baseline flow, determining a mean dose of $\leq$26 Gy to recover the initial flow rate at 12 months [15,16]; this threshold value varies between studies. The threshold can also be determined on a dose-volume histogram (a decision-making tool in radiotherapy; see Fig. 1) in terms of the percentage (e.g., 50%) of the contralateral parotid gland receiving >30 Gy radiation. The other salivary glands, such as the accessory glands, also contribute to non-stimulated flow and to chronic dry mouth, but have as yet been little studied.

Evolution of radiation techniques

So-called ''cobalt bombs'' have been withdrawn from the technical arsenal in France: although useful in certain superficial tumors, they did not allow precise dose adjustment with respect to cutaneous and mucosal toxicity, which was high. Cobalt therapy was therefore gradually replaced by 3D conformal techniques (3D-CR), including intensity-modulated conformal radiation therapy (IMRT). Multi-leaf collimators (MLC) are one of the major innovations of the last 30 years: initially designed to replace the individualized lead caches focusing the beam, they contributed to the development of conformal radiation therapy and to the derivative applications involving beam modulation that led to IMRT.

IMRT

IMRT has been used in France since the first decade of this century, at first for rhinopharyngeal and oropharyngeal cancer and with the aim of conserving salivary function [17]. Most studies have been retrospective and non-randomized, as the technique quickly came into routine use. Some studies focused on salivary flow, but often with non-standardized measurement methods and sometimes without taking locoregional control into account, although the goal of conserving salivary function is applicable only to the extent that oncological control is not impaired. The advantage of IMRT and its derivatives (arc therapy and tomotherapy) is to generate isodoses that are ''sculpted'' to complex concave forms, with better conformation than in 3D radiation. This ballistic advantage serves well in the treatment of lateralized and/or early-stage tumor, to conserve salivary function where oncologically feasible, or on the other hand to treat locally advanced tumors in which it would be impossible to deliver a full dose to the entire tumor volume in 2D due to neighboring structures such as the bone-marrow in case of tumor fixed to the prevertebral planes. IMRT reduces the high-dose volume and may reduce the rate of complications. It also allows dose escalation, so as to enhance oncologic efficacy [18—20]. These advantages remain to be demonstrated clinically in prospective randomized comparative studies versus standard 3D techniques, and should result in an improvement in quality of life.

To ensure precision of treatment and constant positioning, restraints such as masks, arm-rests and toe clips are used. The schematized principles of IMRT executed in ''step-and-shoot'' (stopping the shoot at each leaf movement) or ''dynamic'' mode (continuous shooting simultaneous to the collimator movements) are based on increasing the beam number (five to nine, instead of three as in 2D radiation) and number of entry points (e.g., anterior beam), and implementing dose fluence (number of photons per unit area per unit time) (Fig. 2): i.e., voxel-by-voxel dose modulation. Modulation is achieved by mobilizing the MLCs to achieve a specific dose distribution voxel-by-voxel within each beam. The resultant dose gradients are steep, unlike with radiation using two opposing parallel beams resulting in a homogeneous ''tunnel'' dose distribution. IMRT implements a novel inverse planimetric principle: clinical