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Original article

Real-life efficacy of volumetric modulated arc therapy in head and neck squamous cell carcinoma

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ABSTRACT

Objectives: There is paucity of data on the efficacy of volumetric modulated arc therapy (VMAT) in head and neck squamous cell carcinoma (HNSCC). The objective of the present study was to investigate outcomes and patterns of recurrence in locally advanced HNSCC treated by VMAT.
Methods: A retrospective study included all patients with stage III or IV HNSCC undergoing curative VMAT.
Results: From 2010 to 2013, 130 patients were treated for locally advanced oropharynx ($n = 55$; 42%), hypopharynx ($n = 38$; 29%), larynx ($n = 22$; 17%) or oral cavity ($n = 15$; 12%) SCC. Median age was 60 years (range, 39–85). Median follow-up was 18.1 months (range, 0–43.7). By end of follow-up, 60 patients (46%) had died. Two-year progression-free and overall survival were respectively 63.6% and 77.3% for laryngeal tumors, 60% and 60% for oral cavity tumors, 52.6% and 57.6% for oropharyngeal tumors, and 38.8% and 54.7% for hypopharyngeal tumors. Most recurrences were located within or marginal to radiation therapy fields.
Conclusion: This retrospective analysis is, to our knowledge, the largest study of the efficacy of VMAT in HNSCC. Recurrence patterns and outcomes were consistent with those previously reported for intensity-modulated radiotherapy.

1. Introduction

Radiation therapy (RT) with or without concomitant chemotherapy is a keystone in the treatment of locally advanced head and neck squamous cell carcinoma (HNSCC). Over the past 20 years, major technical advances have improved the efficacy/toxicity ratio of RT. Intensity-modulated radiation therapy (IMRT) is the current standard of care in HNSCC RT, in the light of Nutting's phase 3 randomized controlled trial [1]. However, longer treatment time than with conventional RT is an important limitation of IMRT: inevitable patient movement during treatment may impair peripheral tumor coverage, leading to marginal recurrence. The recently developed volumetric modulated arc therapy (VMAT) considerably reduces treatment time. VMAT is not just a rotational form of IMRT: dose delivery rate, gantry speed and multi-leaf collimator position can be varied continuously during the RT session. Doses can thus be delivered with better conformation, to reduce toxicity. The dose delivery rate is also significantly increased, enhancing the biological effect. While dosimetric studies have shown the advantages of VMAT over IMRT in HNSCC, there is paucity of data on clinical impact on organs at risk (OAR), and above all on efficacy [2]. A retrospective study of heterogeneous HNSCC patients showed no tendency for toxicity to rise, either in postoperative or exclusive VMAT [3], as might have been feared due to the "dose-bath" phenomenon. However, VMAT requires a learning curve for optimal performance, and does not seem to be able to completely spare essential OARs such as the salivary glands [4]. No phase 3 prospective randomized trials comparing IMRT versus VMAT have been conducted, and it is of great interest to report data on the efficacy of VMAT in order to evaluate its real therapeutic index.

The aim of this study was to report retrospective data on efficacy and outcome in locally advanced HNSCC patients receiving VMAT as part of overall management.

2. Materials and methods

A retrospective study was conducted at the Lucien-Neuwirth comprehensive cancer care center (Saint-Priest-en-Jarez, France).

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The institutional review board approved the study, which was conducted in compliance with the Helsinki Declaration.

2.1. Patient population

Medical records of consecutive patients receiving VMAT with curative intent for histologically proven non-metastatic locally advanced squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx between 2010 and 2013 were retrospectively reviewed. Patient characteristics (age, gender, toxic habits), treatment history (surgery, induction chemotherapy [ICT]), tumor characteristics (location, staging, histology, cell differentiation, human papillomavirus [HPV] infection), RT characteristics (prescribed dose, treated locations, mean and maximum administered dose, volume coverage, fractionation, total treatment time), and concomitant medication (chemotherapy, targeted therapy) were reported. Tumors were staged according to the AJCC 7th edition [5]. All cases were presented at the institution's multidisciplinary head and neck tumor board prior to treatment initiation. Prior induction chemotherapy (ICT) or surgery was not exclusion criteria. Three cycles of ICT (docetaxel 75 mg/m^2 day 1, cisplatin 75 mg/m^2 day 1, and 5-fluorouracil 750 mg/m^2 days 1–5) at 3-week intervals were prescribed as part of larynx-sparing protocols and could be considered for patients with very advanced bulky tumor inaccessible to surgery. Surgery was performed after ICT when tumor response was less than 80%. Concomitant postoperative RT-chemotherapy was performed in patients with high risk of failure [stages T3–T4 > 3 cm ipsilateral lymph node and/or bilateral lymph nodes, invaded resection boundaries (R1) and/or nodes with extra capsular extension (ECE) on pathology report].

2.2. Treatment definition

Management of locally advanced HNSCC could comprise: optional primary surgery followed by RT, optional primary surgery followed by concomitant platinum-based or cetuximab chemotherapy and RT, induction chemotherapy followed by optional surgery and RT, or induction chemotherapy followed by optional surgery followed by concomitant platinum-based or cetuximab chemotherapy and RT. Lymph node dissection (LND) was not considered as surgery.

2.2.1. Concomitant chemotherapy

RT could be performed with concomitant chemotherapy or molecular targeted therapy (cetuximab). Chemotherapy consisted of intravenous infusion of cisplatin every week (40 mg/m^2) or every 3 weeks (100 mg/m^2). In case of renal dysfunction, carboplatin replaced cisplatin. In case of contraindications to platinum-based chemotherapy (poor general health status or multiple comorbidity), cetuximab 400 mg/m^2 was administrated one week before RT, then 250 mg/m^2 weekly until end of RT.

2.2.2. Radiation therapy

Patients were treated in supine position and immobilized using a thermoplastic mask covering head and shoulders. Treatment planning was based on CT scan with slice thickness of 2.5 mm. CT images were acquired from the top of the vertex to the carina, without contrast enhancement. Delineation and calculation used the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA). VMAT used one or two 6-MV arcs modulated by a dynamic multi-leaf collimator (Varian Medical Systems, Palo Alto, CA).

2.2.2.1. Volume definition. Gross tumor volume (GTV), clinical tumor volume (CTV), planning tumor volume (PTV) and OARs were delineated based on the planning CT scan. Gross tumor volume (GTV) included primary tumor volume and invaded cervical lymph nodes. Primary tumor extent was assessed on physical examination, videolaryngoscopy and diagnostic imaging. Lymph node involvement was suspected on abnormal enlargement on CT imaging or abnormal uptake of radiolabeled [^{18}F]-2-fluoro-deoxy-D-glucose (FDG) on PET/CT imaging. CTV was calculated by adding variable margins to the GTV, depending on tumor location [6–8]. Post-resection CTV was delineated as defined in literature [7–9]. At least 3 different CTVs were defined for each patient. Tumor CTV (CTV T) comprised the primary tumor volume or postoperative tumor bed site plus margins. High-risk node clinical tumor volume (CTV HRN) comprised unresected macroscopically involved nodes and/or ablated nodes with ECE on pathology reports, plus margins. Low risk node CTV (CTV LRN) included suspected microscopically involved nodes, plus margins. Prophylactic node CTV (CTV PN) could also be delineated, comprising non-involved at risk node regions, depending on primary tumor location [10–13]. PTV was generated by adding a 5 mm margin to the CTV.

2.2.2.2. Dose prescription. For non-operated patients, a dose of 66–70 Gy was prescribed for the PTV T in 30–35 fractions at 2–2.2 Gy per fraction. Then, 60–66 Gy was prescribed for the PTV HRN in 30–33 fractions at 2–2.2 Gy per fraction; 60 Gy was prescribed for the PTV LRN in 30 fractions at 2 Gy per fraction; 50 Gy was prescribed for the PTV PN in 25 fractions. For operated patients, 66 Gy was prescribed for the primary tumor bed and involved nodes (PTV T) in 33 fractions at 2 Gy per fraction; 60–66 Gy was prescribed for the PTV HRN in 30–33 fractions at 2 Gy per fraction; 50 Gy was prescribed for the PTV PN in 25 fractions. Standard integrated boost (SIB-VMAT) could be used, with fractionation as described in the literature [10–12]: 66 Gy (2.2 Gy/fraction) for PTV T, 60 Gy (2 Gy/fraction) for PTV HRN, and 54 Gy (1.8/fraction) for PTV LRN. Treatment plans were optimized according to dose limits for OARs and requirements for volume coverage: i.e., PTV should receive 95% to 107% of the prescribed dose, and PTV coverage should be higher than 95%. International Commission on Radiation Units and Measurements guidelines (ICRU 83 report) were applied [13]. Dose–volume histograms (DVH) were systematically reviewed by a radiotherapist.

2.3. Efficacy assessment

Follow-up was calculated from the end of RT. Patients were clinically assessed for efficacy every week during RT, then every 3 months for 2 years and every 6 months for another 3 years. Imaging (contrast-enhanced head and neck and thorax-abdomen-pelvis CT ± PET/CT) and video-endoscopy were performed every 6 months. Infield relapse was defined as tumor recurrence in the area that received 95% of the prescribed dose (95% isodose). Marginal relapse was defined as tumor recurrence in the area that received 20% to 95% of the prescribed dose (20–95% isodose). Tumor progression was defined as non-regression of the tumor within 3 months following the last RT fraction. Progression-free survival (PFS) was defined as the time from histological diagnosis to the date of diagnosis of clinical and/or radiological disease progression and/or death by any cause. Overall survival (OS) was defined as the time from histological diagnosis to the date of death.

2.4. Statistical analysis

Median values with range and mean values with standard deviation were calculated. Statistical analyses used R 3.1.1 software (R Core Team, 2013, R Foundation for Statistical Computing, Vienna, Austria).

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