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Lymph node metastases

Unilateral neck irradiation for well-lateralized oropharyngeal cancer

Abrahim Al-Mamgani [a,*], Peter van Rooij [b], Dennie Fransen [a], Peter Levendag [a]

[a] Department of Radiation Oncology, Erasmus MC-Daniel den Hoed Cancer Center, Rotterdam, The Netherlands; [b] Department of Biostatistics, Erasmus MC-Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

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ABSTRACT

Background and purpose: To investigate the impact of unilateral neck irradiation (UNI) of well-lateralized oropharyngeal cancer (OPC) on outcome and toxicity.
Materials and methods: Unilateral neck IMRT was applied to 185 consecutive patients with well-lateralized OPC (restricted to tonsillar fossa, soft palate with at least 1 cm from midline or lateral pharyngeal wall). Endpoints were regional control (RC), local control (LC), disease-free survival (DFS), overall survival (OS), and toxicity.
Results: Six regional failures were reported (3.2%); 2 were contralateral (1.1%). The 5-year Kaplan–Meier estimates of RC, LC, DFS, and OS were 96%, 91%, 84%, and 70%, respectively. Feeding tube was given to 11.3%. Chemotherapy was significantly predictive for toxicity. However, no patient was still feeding tube dependent 6 weeks after treatment. Overall grade 3 late toxicity was 2.2%. Grade 3 xerostomia was reported in only 1 patient while no patient developed grade 3 dysphagia.
Conclusion: This largest study on unilateral neck IMRT for well-lateralized OPC showed excellent outcome and favorable toxicity profile. Given the increasing incidence of OPC, especially among younger patients, and the favorable results reported in the current study and by other investigators, expanding the indications for UNI still needs to be further investigated in prospective, preferably, randomized trials.
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Well-lateralized oropharyngeal cancers (OPCs) are characterized by a relatively orderly spread to cervical lymph nodes. Studies where the pattern of regional failure (RF) was analyzed suggested a very low incidence of contralateral RF from well-lateralized tumors [1]. It is generally accepted that elective neck irradiation is not recommended when the risk of subclinical disease is less than 15%. There is slowly growing evidence in the literature supporting the unilateral neck irradiation (UNI) in early-stage OPC without compromising loco-regional control (LRC) [2–4]. However, the definition of well-lateralized tumor and the criteria for inclusion of patients for UNI were not identical in these studies.

Given the relative paucity of data regarding the impact of UNI on oncologic outcome and toxicity of patients with well-lateralized OPC, our aim is to report our institutional experience with unilateral neck IMRT, to compare our results with those of other investigators and to review the literature in order to identify subgroups of patients where UNI is objectively justified.

Materials and methods

From January 2000 to June 2011, 659 consecutive patients with OPC were treated at our institution. Of them, 185 patients had a well-lateralized OPC (T1-3N0-2b) and were treated with UNI and are the subject of this study.

Pre-treatment evaluations consisted of complete history and physical examination, including direct laryngoscopy under general anesthesia. All patients had a chest X-ray, ultrasound with FNA, head and neck MRI or CT scan. In case of any doubt about the tumor and/or nodal staging, FDG-PET scan was performed. All patients were presented at our weekly multidisciplinary head and neck conference. Based on the joint recommendations of the multidisciplinary meeting, patients selected for UNI were those with a well-lateralized OPC; defined as tumors confined to the tonsillar fossa, the soft palate with at least 1 cm from the midline or the lateral pharyngeal wall.

Radiotherapy

Patients were immobilized in supine treatment position in a custom-made head and neck mask. CT-scan simulation was performed in all patients. The CTV consists of the delineated GTV on contrast-enhanced planning-CT and the involved node level(s) plus margin of 5 mm. The PTV included a margin of 5 mm beyond the

* Corresponding author. Address: Department of Radiation Oncology, Erasmus MC-Daniel den Hoed Cancer Center, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands.
E-mail address: a.al-mamgani@erasmusmc.nl (A. Al-Mamgani).

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CTV of the primary tumor and the ipsilateral neck to account for different targeting uncertainties. The treatment of well-lateralized OPC at our institution consists of a first series of 46-Gy of step-and-shoot IMRT to the primary tumor and ipsilateral neck (23 * 2 Gy, 6 fractions/week), followed by a brachytherapy boost to the primary tumor (22-Gy). Before 2005, patients not suitable for brachytherapy boost (gross tumor >5 cm, tumor adjacent to the mandible or large vessels, tumors invading retropharyngeal of parapharyngeal spaces, major comorbidity, logistical problems or because of a combination of these factors), received a boost by means of IMRT (12 * 2 Gy, 6 fractions/week). In 2005, a stereotactic body radiotherapy system (Cyberknife®, Accuray Inc., Sunnyvale, CA, USA) was installed in our institution. Cyberknife® is able to deliver a conformal dose distribution because of the rapid fall-off outside the target volume; an almost identical dosimetry to that which is accomplished by a brachytherapy planning. Since May 2005, patients with OPC not suitable for brachytherapy boost, received a boost to the primary tumor by means of Cyberknife (3 * 5.5 Gy on consecutive days) (Table 1). The details of these boost techniques were published previously [5,6].

According to our institutional protocol, the treatment of the neck consists of 46-Gy of IMRT to the ipsilateral neck, in case of node-negative disease. In case of N^+, neck dissection (ND) was performed after 46-Gy of IMRT in the involved neck. In case of brachytherapy boost, the ND was performed before implantation of the catheters for brachytherapy while in case of Cyberknife boost, it was performed after finishing the boost. Patients unsuitable for brachytherapy or Cyberknife boost were treated with 70-Gy of IMRT to the primary tumor and the involved neck and did not undergo ND. When chemotherapy was indicated (T3), two cycles of cisplatin were given (100 mg on days 1 and 22 of radiotherapy).

Table 1
Patient's characteristics & treatment data (n = 185).

	No. of patients (%)
Gender	
Male	126 (68%)
Female	59 (32%)
Age (years)	
Range	37–85
Median	57
Follow-up (months)	
Range	4–127
Median	49
Tumor stage	
T1	50 (27%)
T2	122 (66%)
T3	13 (7%)
Nodal stage	
N0	92 (50%)
N1	43 (23%)
N2a	18 (10%)
N2b	32 (17%)
Tumor subsite	
Tonsillar fossa	129 (70%)
Soft palate	47 (25%)
Lateral pharyngeal wall	9 (5%)
Neck dissection	
Yes	80 (43%)
No	105 (57%)
Chemotherapy	
Yes	11 (6%)
No	174 (94%)
Dose & technique radiotherapy	
46 Gy IMRT + 24 Gy IMRT boost	40 (22%)
46 Gy IMRT + 22 Gy PRD BTB	116 (63%)
46 Gy IMRT + 16.5 Gy CK boost	29 (15%)

Abbreviations: IMRT, intensity-modulated radiotherapy; PDR BTB, Pulse Dose Rate brachytherapy boost; CK, Cyberknife.

Endpoints

Endpoints of the study were rates of regional control (RC), local control (LC), disease-free survival (DFS), overall survival (OS), acute and late toxicity, and QoL.

Regarding local (LF) and regional failure (RF), the first time recurrence was reported, this was registered as the date of failure. The ultimate local and regional control rates reflect the proportion of patients primarily cured by radiotherapy added to those who were successfully salvaged after local or regional recurrence. DFS was measured from the date of completion of treatment to the date of first relapse (local, regional or distant).

Acute toxicity ($\leqslant$90 days after treatment) was evaluated by the radiation oncologist during the weekly visit of patients to our outpatients' department. Late toxicity (>90 days after treatment) scores were prospectively collected using Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

Follow-up

The treatment response was evaluated by clinical examination 6–8 weeks after completion of treatment and by MRI or CT-scan 12 weeks after treatment. On completion of treatment, patients were followed up 2-monthly for the first year, 3-monthly for the second and third years and 6-monthly thereafter. At each visit, history and clinical examination were performed, including flexible nasoendoscopy.

Statistical analysis

Survival rates were calculated from the completion of treatment using the Kaplan–Meier technique. Possible predictive factors for LF and toxicity were tested using exact logistic regression model. The Mann–Whitney sign test was used for non-parametric significance tests. All significant tests were two-sided and p values <0.05 were considered statistically significant.

Results

Outcomes

Thirty events were reported: 6 RF, 16 LF, and 8 distant failures, resulting in crude RC, LC, DMFS, and DFS rates of 97%, 91%, 96%, and 84%, respectively. The median time from treatment completion to local–regional recurrence or DM was 11 months (range, 3–80).

After a median follow-up of 49 months (range, 4–127), the 5-year Kaplan–Meier estimates of RC, LC, DFS, and OS were 96%, 91%, 84%, and 70%, respectively (Fig. 1).

Only 6 patients developed RF (3.2%), 2 of these were contralateral recurrences (1.1%). All RFs were successfully salvaged with surgery and postoperative radiotherapy, resulting in an ultimate RC-rate of 100%. All those patients were still alive at the time of the last follow-up without evidence of disease progression. No univariate analysis was done to identify clinical or pathological factors predictive for RF, because of the small number of failures reported in the present study. Table 2 illustrates characteristics of patients with RF.

Sixteen patients developed LF (8.6%), 7 of these were salvaged by surgery, resulting in an excellent ultimate LC-rate of 95%. All other patients with LF had an advanced recurrence and were inoperable and eventually died from their local disease progression. On univariate analysis, none of the tested variables correlated significantly with LF. Only T-stage showed a trend toward significant correlation; LF rates for T1, T2, and T3 were 5.2%, 9.1%, and 15.8%, respectively (p = 0.07).

Eight patients developed DM, mainly to the lung, bone and/or brain. One patient with lung metastasis was salvaged by surgery