Radiotherapy and Oncology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

High-dose reirradiation with intensity-modulated radiotherapy for recurrent head-and-neck cancer: Disease control, survival and toxicity ☆

Fréderic Duprez [a,*], Dieter Berwouts [a], Indira Madani [a], Katrien Bonte [b], Tom Boterberg [a], Werner De Gersem [a], Philippe Deron [b], Wouter Huvenne [b], Wilfried De Neve [a]

[a] Department of Radiotherapy; [b] Department of Head & Neck Surgery, Ghent University Hospital, Belgium

ARTICLE INFO

Article history:
Received 2 October 2013
Received in revised form 14 April 2014
Accepted 22 April 2014
Available online xxxx

Keywords:
Head-and-neck cancer
Radiotherapy
IMRT
Reirradiation
Toxicity

ABSTRACT

Purpose: To evaluate disease control, survival and severe late toxicity after high-dose fractionated reirradiation using intensity-modulated radiotherapy (IMRT) for recurrent head-and-neck cancer.
Materials and methods: Sixty consecutive patients were reirradiated with IMRT between 1997 and 2011. The median prescribed dose was 70 Gy in 35 daily fractions until 2004 and 69.12 Gy in 32 daily fractions thereafter. The median cumulative dose was 132 Gy. Sixty-seven percent of patients had non-metastatic stage IV disease. Surgery prior to reirradiation and concomitant systemic therapy was performed in 13 (22%) and 20 (33%) patients, respectively.
Results: Median follow-up in living patients was 18.5 months. Actuarial 1-, 2- and 5-year locoregional control was 64%, 48% and 32%, respectively. Median overall (OS) and disease-free survival was 9.6 and 6.7 months, respectively. Actuarial 1-, 2- and 5-year OS was 44%, 32% and 22%, respectively. Seventeen (27%) and 2 (3%) patients had grade 3 and 4 acute toxicity, respectively. Cumulative incidence of late grade $\geqslant 3$ toxicity was 23%, 27% and 66% at 1, 2 and 5 years, respectively. In 4 patients, death was attributed to toxicity: fatal bleeding ($n = 2$), aspiration pneumonia ($n = 1$) and skin necrosis ($n = 1$).
Conclusions: High-dose fractionated reirradiation with IMRT offers 5-year disease control and OS in recurrent head-and-neck cancer for 1/3 and 1/4 patients, respectively. Severe late toxicity after 1–2 and 5 years occurs in 1/4 and 2/3 patients, respectively.
 Radiotherapy and Oncology xxx (2014) xxx–xxx

Despite treatment intensification for locoregionally advanced head-and-neck cancer using primary or post-operative concomitant radiochemotherapy, approximately 50% of patients develop locoregional relapse [1]. If technically and medically possible, salvage surgery is the best treatment option resulting in a modest 36% disease-free (DFS) and 36% overall survival (OS) rates at 2 and 5 years, respectively [2]. A multicentric prospective phase-III trial reported 2-year locoregional control (LRC) rates around 20% in surgically salvaged patients after surgery alone and up to 55% if followed by adjuvant reirradiation combined with hydroxyurea and 5-fluoro-uracil [3].

However, salvage surgery as well as brachytherapy is often not an option due to tumor extent, location or other factors [4]. In those patients, palliative systemic treatment (cisplatin, 5-fluoro-uracil and cetuximab) is the current standard of care resulting in median DFS and OS rates of only 5.6 and 10.1 months, respectively [5]. However, the portion of patients that could be cured with systemic therapy as a single modality, probably remains negligible. High-dose reirradiation using external beam radiotherapy can be used as an alternative with curative intent albeit at a risk of important toxicity, e.g. carotid blow-outs that have been observed in up to 8% of patients and treatment related death up to 20% [6–8] as well as other severe toxicity such as dysphagia, fibrosis and necrosis. A prospective RTOG-study in non-surgically salvaged patients using 3D-conformal radiotherapy concurrent with cisplatin-5-fluorouracil demonstrated modest median OS rates of 8.5 months and 1- and 2-year OS of 41% and 15%, respectively. In that trial, only 3 of 32 patients living > 1 year experienced grade $\geqslant 3$ late toxicity [9]. Reirradiation using intensity-modulated radiotherapy (IMRT) demonstrated to bear the potential to be less toxic and more effective than with older radiation techniques but late toxicity remains a problem [10–12].

Previously, we reported 5-year OS rates of 20% and late severe toxicity rates of 50% in 84 patients treated with IMRT with recurrent and second primary head-and-neck cancer [10]. Reirradiation for second primary head-and-neck cancer has resulted in better disease control and survival compared to recurrent head-and-neck

☆ Parts of this material have been presented at the Fourth International Congress in Head-and-Neck Oncology, February 7–9, Barcelona, Spain.

* Corresponding author. Address: Department of Radiotherapy, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium.
E-mail address: frederic.duprez@uzgent.be (F. Duprez).

http://dx.doi.org/10.1016/j.radonc.2014.04.018
0167-8140/

cancer, as in the latter group, radioresistance might be among the causes of recurrence [11,13]. In this retrospective study, we report long-term treatment results (LRC, survival and severe toxicity). The purpose is to gain insight in long-term severe toxicity and chances for disease control after high-dose reirradiation for recurrent head-and-neck cancer in order to inform patients based on a relatively large case series, using IMRT and with long-term follow-up. These results can help to decide which therapy could be chosen, i.e. palliative systemic therapy vs. high-dose fractionated IMRT.

Materials and methods

Patient selection and characteristics

Data on patients with recurrent carcinoma of the oral cavity, pharyngeal, laryngeal and paranasal sinuses as well as nodal neck recurrences who started high-dose reirradiation (>60 Gy) using IMRT in our hospital between June 1997 and September 2011, with at least 6 months of follow-up after IMRT (unless they deceased before), were retrieved. Second primary tumors were excluded. Second primary tumors were defined as tumors arising in other sites than the first tumor, or arising >30 months after the previous treatment and in case of doubt between a second primary tumor or a recurrent head-and-neck cancer, the decision was taken in our multidisciplinary staff meetings. All patients underwent physical examination by dedicated head-and-neck surgeons, computed tomography (CT) and/or magnetic resonance imaging of the head and neck region and chest radiography or CT. The decision for reirradiation with IMRT was taken after multidisciplinary discussion and based on the following criteria: (1) histological confirmation of recurrent carcinoma, (2) absence of distant metastases, (3) impossibility of salvage surgery or brachytherapy, (4) macroscopically incomplete salvage surgery or (5) patient refusal of surgery.

Sixty consecutive patients fulfilled the inclusion criteria (Table 1). The median time interval between previous radiotherapy and reirradiation was 27 in a range of 6–240 months. Almost half of patients (48%) had stage T4 and two thirds (67%) of patients had stage IVA/B disease. Thirteen patients (22%) with stage IVA/B non-sinonasal recurrent cancer received concomitant systemic treatment (platinum-based in $n = 11$ before June 2004 and cetuximab in $n = 1$ in 2011). Twenty patients (33%) received post-operative reirradiation.

Table 1
Patients and tumor characteristics.

Characteristic	$n = 60$	%
Gender		
Male	53	88
Female	7	12
Age (years)		
Median	56	
Range	36–77	
Site		
Oral cavity	15	25
Oropharynx	14	23
Sinonasal	12	20
Larynx	7	12
Neck	5	8
Nasopharynx	4	7
Hypopharynx	3	5
T-stage		
T0	11	18
T1	5	8
T2	9	15
T3	4	7
T4	29	48
T unspecified	2	3
N-stage		
N0	33	55
N1	9	15
N2a	4	7
N2b	5	8
N2c	6	10
N3	2	3
N unspecified	1	2
Stage grouping		
I–III	20	33
IV	40	67
Histology		
Squamous cell carcinoma	46	77
Adenocarcinoma	9	15
Nasopharyngeal carcinoma	2	3
Unspecified	3	5

Target definition

Contrast-enhanced planning-CT of the head and neck was performed in treatment position with a thermoplastic mask and neck support. Since 2006, all patients ($n = 15$), except those with sinonasal tumors underwent a [18F]fluoro-2-deoxy-D-glucose positron emission tomography ([18F]FDG-PET) in treatment position. Co-registration with magnetic resonance imaging was performed in patients with sinonasal tumors. A 0.5–1.5 cm isotropic expansion of the gross tumor volume (GTV) encompassing tumor and/or pathological lymph nodes resulted in the clinical target volume (CTV). In case of surgery the CTV encompassed the post-operative tumor bed. The CTV was expanded isotropically with a 3 mm margin to a planning target volume (PTV). The elective neck was irradiated in 17 patients between 1997 and 2005 (28%) and was omitted since 2006. The spinal cord, brainstem, parotid glands and mandible were outlined as OARs. Expansion of spinal cord and brainstem with a 3–5 mm margin resulted in the respective planning organ-at-risk volumes (PRVs).

Dose prescription and treatment delivery

The median prescribed dose to the target was 70 Gy in 35 fractions over 7 weeks until December 2004 and thereafter 69.12 Gy in 32 fractions over 6.5 weeks. In all sinonasal recurrences, the prescription dose was 70 Gy in 35 fractions. In the case of elective neck irradiation ($n = 17$), simultaneous integrated boost to the high dose target was used with neck doses ranging between 50 and 62 Gy.

Dose constraints for organs-at-risk have previously been described and did not change since then [10]. In brief, hard constraints were only applied for the spinal cord and brainstem PRV's: the implemented formulas are $[D_{50} < (x\text{Gy} - \frac{1}{2}\text{Dp})]$ and $[V(y\text{Gy} - \frac{1}{2}\text{Dp}) < 5\%]$, in which x and y are 45 and 50 for spinal cord respectively, and 50 and 60 for brainstem, respectively, and D_{50} = median dose; ½Dp = a half of the previously delivered (i.e. >1 year interval) maximum dose to the organ at risk; Vy = relative volume of the organ at risk receiving at least yGy.

Follow-up and statistical analysis

All patients were followed up three-monthly for the first year, four-monthly in the second year, biannually in the subsequent years and from 5 years on annually. In case of suspicion of recurrence, MRI or CT was performed and if possible histological confirmation by biopsy was obtained. Late toxicity was defined as toxicity persisting or occurring at $\geqslant$6 months post-IMRT and was scored using the LENT-SOMA scale at each patient visit [14]. Only grade $\geqslant$3 late toxicity was considered for this study.

Locoregional and distant control were defined as the absence of locoregional recurrence or progression and distant metastases

Please cite this article in press as: Duprez F et al. High-dose reirradiation with intensity-modulated radiotherapy for recurrent head-and-neck cancer: Disease control, survival and toxicity. Radiother Oncol (2014), http://dx.doi.org/10.1016/j.radonc.2014.04.018