Re-irradiation in head and neck cases using IMRT technique: a retrospective study with toxicity and survival report

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Abstract

Purpose
The incidence of recurrence after radiation therapy or appearance of secondary primary tumours is not minimal. The aim of this study is the evaluation of survival and toxicity in patients after intensity-modulated radiation therapy (IMRT) re-irradiation due to relapsed head and neck carcinoma.

Methods and materials
In a retrospective manner, we studied 15 patients who underwent IMRT re-irradiation, from January 2007 to March 2012, due to histological proof of recurrent disease or second primary tumour in head and neck area after previous irradiation and no evidence of distal metastases. The median follow-up was 45 months. The combined Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer criteria were employed to assess acute and late toxicity.

Results
At the time of last follow-up, 12 (80%) patients had no evidence of disease and 3 patients had died due to brain or lung metastases and mediastinum lymphadenopathy. Two patients had relapses within the irradiated area 2 years after re-irradiation. The median overall survival and relapse-free survival were 35 and 45 months, respectively. A correlation was noted (Spearman $p = 0.52$, $P = 0.047$) between acute mucositis of re-irradiation and summation dose (previous and second course). In terms of acute toxicity, three (20%), two (13.3%) and nine (60%) patients presented grade III, II and I acute mucositis, respectively, and two (13.3%), nine (60%) and four patients (26.6%) presented grade III, II and I acute skin toxicity, respectively. Oedema of the larynx and fungal infection of the pharynx were observed in all cases. Late radiation toxicities were observed in seven patients: paralysis of true vocal cord, which needed laryngoplasty in one patient, two patients had odynofagia, one patient had dysphagia, one patient presented carotid stenosis and two patients presented long-term anorexia.

Conclusion
The IMRT technique allows re-irradiation with safety and tolerated toxicity. However, future prospective studies of these approaches with more number of patients are warranted.

Introduction
Nowadays, overall survival of cancer patients has increased. In head and neck cancer, the incidence of recurrence after radiation therapy or second primary tumours is 30%–50% and 20%, respectively. As a consequence, locally recurrent tumours, second primary tumours in the head and neck region need to be treated. Moreover, metastatic spinal cord compression occurs in 5%–10% of all cancer patients during the course of their disease. The gold standard after previous radiotherapy is salvage surgery. When the tumour is inoperable and chemotherapy cannot offer local control (LC), radiation therapy seems to be the only solution. However, there is a definite dose limit not only for the tumour itself but also for the surrounding critical organs. Spinal cord injury especially results in pain, paresthesias, sensory deficits, paralysis, Braun–Sequard syndrome, bowel or bladder incontinence and Lhermitte syndrome.

In this study, we analysed the effectiveness of re-irradiation for head and neck cancer with regard to toxicity, locoregional control and overall survival (OS). All patients with previous radiation treatment to the head and neck area and recurrence or secondary primary tumour were included in this retrospective study.

Material and methods
From January 2007 to March 2012, in a retrospective manner, we studied 15 patients with histological proof of recurrent disease or second primary tumour after previous irradiation and no evidence of distal metastases. The pre-treatment diagnostic evaluation included magnetic resonance imaging (MRI) for the head and neck region and positron emission tomography–computed tomography (PET-CT) for distant metastases. Patients with unresectable disease and primary irradiation were discussed by a multidisciplinary oncologic board. In patients...
with recurrent disease, the minimum time interval between previous radiotherapy and re-irradiation was 2 years, unless the tumour area was in a non-irradiated region. Post-operative irradiation was applied either if the surgical margins were positive or if there were lymph node involvement and extracapsular extension. Patient and tumour characteristics are shown in Table 1.

**Radiotherapy treatment**

The treatment was given with a 6 MV photon linear accelerator using an immobilization mask. Intensity-modulated radiation therapy (IMRT) was applied via step and shoot technique in conjunction with multi-leaf collimator. IMRT treatment planning was performed by the Oncentra Masterplan (4.1 Nucletron, the Netherlands) (Figure 1).

The spinal cord was considered as the most important organ at risk during re-irradiation. For all cases, the maximum dose for spinal cord was designed to be between 12 Gy and 16 Gy, with the exception of patients irradiated at least 15 years ago. These latter patients received 50 Gy to the spinal cord and the intent was to keep the cumulative biological equivalent dose below 130 Gy. All patients received their first irradiation with standard parallel opposing fields in other hospitals and then they were referred to our department. All information concerning the dose of the spinal cord was available except the doses of other organs at risk (OAR) such as mandible, oral cavity, great cervical vessels, cranial nerves and cervical nerves. Due to the lack of previous information, the doses for these OAR were kept as low as possible.

The gross tumour volume (GTV) definition for re-irradiation included the tumour itself and the positively diagnosed (using PET-CT) lymph nodes. A margin of 1.5 cm was applied to GTV in order to include the clinical target volume (CTV). In all patients, elective areas with a reasonable risk for microscopic disease, such as the ipsilateral or contralateral neck levels, were defined as different CTVs. In patients who underwent surgery, the CTV included the surgical resection bed with 1.5 cm of safety margins. A margin of 3–5 mm was applied on all CTVs in order to define the planning target volume (PTV) and on account of setup and treatment delivery uncertainty.

The prescribed dose to the elective areas was 46 Gy. The prescribed dose to the high-risk area was 60 Gy, whereas the involved area received 66–70 Gy.

The median delivered dose in the first treatment course was 64 Gy (range = 45–70 Gy). The median delivered dose in the re-irradiation treatment course was 66 Gy (range = 60–70 Gy). The median interval between the first and the second treatment courses was 52 months (range = 24–228 months).

In all patients, concurrent chemotherapy with re-irradiation was not given. In three patients, chemotherapy was given before the radiation treatment with cisplatin and 5-fluoracil. All patients signed informed consent regarding the radiation-induced morbidity due to re-irradiation.

**Follow-up**

Patients were followed-up was on a quarterly basis for the first 12 months, semi-annually for the next 2 years and then annually.

Acute toxicity was assessed on a weekly basis during the treatment and 4 weeks post-completion of treatment. Late toxicity was assessed 9 months post-treatment. The maximum score for either acute or late morbidity was chosen as the

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**Table 1** Tumour and treatment characteristics of 15 patients

<table>
<thead>
<tr>
<th>Tumour and treatment characteristics of 15 patients</th>
<th>Number of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>60</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>Median age in years (range)</td>
<td>55 (range = 22–74)</td>
<td></td>
</tr>
<tr>
<td>Primary tumour site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>4</td>
<td>26.7</td>
</tr>
<tr>
<td>Larynx</td>
<td>5</td>
<td>33.4</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>2</td>
<td>13.3</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>2</td>
<td>13.3</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>2</td>
<td>13.3</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>9</td>
<td>60</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>5</td>
<td>33.3</td>
</tr>
<tr>
<td>Basal carcinoma</td>
<td>1</td>
<td>6.7</td>
</tr>
<tr>
<td>Indication for re-irradiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second primary</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>Recurrence</td>
<td>9</td>
<td>60</td>
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<tr>
<td>Re-irradiation setting</td>
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<td></td>
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<tr>
<td>Definitive</td>
<td>10</td>
<td>66.7</td>
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<tr>
<td>Post-operative</td>
<td>5</td>
<td>33.3</td>
</tr>
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</table>

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The combined Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer criteria were employed to assess acute and late toxicity. The follow-up evaluations included clinical examination with laryngoscopy and biopsies where necessary; MRI imaging investigations were performed every 3 months. Distant failure was scored on the basis of radiological or pathological findings. LC was measured from the start of the re-irradiation until recurrence. RFS was defined as the time from the start of re-irradiation until local recurrence (LR), distant metastasis or death.

**Statistical analysis**

The correlation between the irradiation dose and either the acute or late toxicity was performed with Spearman’s ρ non-parametric test. The OS and RFS were calculated with the Kaplan–Meier survival method. In all calculations, the significance level was taken as 0.05. All analyses were done with SPSS software (version 10, Chicago, IL, USA).

**Results**

The median follow-up was 45 months (range = 25–60 months). At the time of last follow-up, 12 (80%) patients had no evidence of disease and 3 patients died due to brain metastases, lung metastases and mediastinal lymphadenopathy. Two patients had relapsed within the irradiated area 2 years after the re-irradiation: one in the larynx and other in the left side of the tongue. They were operated, and so far, they are disease free.

The Kaplan–Meier distribution for both RFS and OS is shown in Figure 2. The median OS and RFS were 35 months and 45 months, respectively. The Spearman’s ρ non-parametric test revealed neither correlation for previous nor for the current dose with the toxicity scores ($P = $ non-significant). However, there was a critical significance ($P = 0.047$) between acute mucositis of re-irradiation and summation dose (previous and second course), with $ρ = 0.52$.

Surprisingly, no correlation was noted between the intermediate time of first and second irradiation and radiation-induced toxicity (mucosal and skin).

**Toxicity and complications after re-irradiation**

Acute toxicity in terms of mucositis was observed in three patients as grade III, in two patients as grade II and in nine patients as grade I. Grade III toxicity to the skin was seen in two patients, whereas grade II skin toxicity was observed in nine patients and four patients had grade I skin toxicity. Oedema of the larynx and fungal infection of the pharynx were observed in our patients but these were resolved with medication.

Late radiation toxicities were observed in seven patients. The most serious side effect was a paralysis of true vocal cord, which needed laryngoplasty in one patient. Two patients had odynophagia and neck pain requiring hospitalization and one patient had dysphagia requiring oesophageal dilatation. In addition, carotid stenosis was observed in one patient and two patients presented long-term anorexia.

The dose of re-irradiation in the spinal cord was recorded in the range of 12–50 Gy (mean = 21.3 Gy, median = 15 Gy).

**Figure 1:** One patient with relapsed head and neck carcinoma in larynx with positive left cervical lymph nodes. The IMRT plan shows a definite sparing of the spinal cord, along with an excellent coverage of the PTV. The dose to the spinal cord was 14 Gy, whereas the prescription dose to the PTV was 60 Gy.
Discussion

The most dangerous side effect of re-irradiation is myelitis. The importance of spinal cord damage reflects on the patient’s quality of life (QOL). Radiation myelopathy is a rare complication and is categorized in three phases: acute (within days to weeks), early-delayed (within weeks to 6 months) and late-delayed (after more than 6 months)\(^1\). Sheline et al. support the view that radiation myelopathy caused by white matter necrosis may develop between 6 months and 7 years\(^2\). Furthermore, there are no studies in humans that have investigated the behaviour of the spinal cord after re-irradiation; therefore, it is necessary to collect reliable data.

Although our study deals with a small series of patients (\(n = 15\)), our patients were treated with curative intent and the median OS was 45 months. No radiation-induced myelitis was observed and the side effects were acceptable, according to the QOL.

In clinical practice, there often exists the need for re-irradiation in tumours arising in the proximity of the spinal cord. The acceptable principle about spinal cord dose constraint is the concept of ALARA (as low as reasonably achievable)\(^13\). In 2010, Kirkpatrick et al. proposed that estimated myelopathy is \(<1\%\) for 54 Gy and \(<10\%\) for 61 Gy, using 1.8–2.0 Gy per fraction, to full thickness cord\(^14\). When cumulative biologically effective dose is \(\leq 120\) Gy, myelopathy seems unlikely\(^9\). In addition, initial radiotherapy schedule has a statistically significant importance on re-irradiation safety\(^5\). Neider et al. are of the opinion that the spinal cord, similar to skin, mucosa and lung, does recover from subclinical injury\(^15\). Genetic factors like mutations in transforming growth factor-\(\beta1\) and ataxia telangiectasia genes may help explain the reason of late effect radiation injury in two re-irradiated patients who received a biologic equivalent dose of only 46 Gy and 81 Gy, with the interval between the courses of radiation being 70–80 months\(^16\). The migratory capacity of oligodendrocyte progenitor cells may have a role in differences in white matter radiation sensitivity\(^17\). Medin and Boike propose that dose distribution of radiation is more critical than the volume irradiated\(^18\). Thus, dose-volume histograms and absolute volume contrains are not effective in predicting complications. Dose-volume tolerance depends on dose rate, irradiated length, irradiated lateral cross section, irradiated region, dose to adjacent spinal cord, previous irradiation and age\(^19\).

In our study, the spinal cord received 50 Gy only in patients who were irradiated at least 15 years ago. In all other patients, the spinal cord received a maximum of 16 Gy, even at the expense of coverage of the PTV. In addition, we observed that the worst acute side effects presented in patients treated with definitive concurrent chemo-irradiation. These patients developed grade III mucositis and severe dysphagia that required hospitalization and intravenous medication. Skin erythema was generally noticed in all cases, whereas neither fistulas nor other co-morbidities were observed. One patient required intravenous medication in the hospital due to an abscess by Aspergillus. We observed a significant improvement in severe chronic morbidity and no patient died from radiation-induced toxicity until now.

Lee et al. studied 74 patients who underwent re-irradiation with the IMRT technique. Improvement in locoregional progression-free and OS outcomes were observed with the application of IMRT. Two years of locoregional control and OS were 19% and 12%, respectively, in patients with unresectable disease. In patients with resectable tumours, the LC and OS were 45% and 36%, respectively. The toxicity was acceptable, with \(4\%\) of chronic neurologic problems\(^19\).

Sulman et al. treated 74 patients with the IMRT technique. At 2 years, the LR control and OS were 58% and 54%, respectively, in patients with unresectable tumours. Acute and

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Original research study
late toxicity (32%) was observed, but there was no fatal side effect. In patients in a post-operative setting, the LC rate and OS were 76% and 68%, respectively. The acute and late side effects were at a level below 25%²⁰.

We observed that techniques like IMRT offer a new approach in spinal cord re-irradiation. Image-guided radiation therapy/IMRT is a technological vehicle that provides to an oncologist with an opportunity to give very high dose of radiation within close proximity of the spinal cord. The IMRT technique in head and neck re-irradiation is able to retain the patient’s QOL and does away with any harmful intervention. It allows re-irradiation with safety and tolerated toxicity. However, due to the lack of homogeneity of our cases and the retrospective nature of our study, conclusions must be drawn with caution. Nevertheless, prospective studies of these approaches are required.

References