# Outcome after Re-Irradiation of Head and Neck Cancer Patients

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**Purpose:** To retrospectively report the outcome of head and neck cancer patients following re-irradiation.
**Patients and Methods:** A total of 51 patients with recurrent or second primary head and neck cancer received re-irradiation at Leuven University Hospital. Survival and locoregional control were calculated. Doses to organs at risk were retrieved from dose–volume histograms. Radiation-related toxicities were reported.
**Results:** The 2-year actuarial overall survival rate was 30%. On univariate analysis, surgery before re-irradiation and high radiation dose were associated with superior survival. Grade 3 acute and grade 3 or more late toxicity occurred in respectively 29.4% and 35.3% of the patients.
**Conclusion:** Re-irradiation in head and neck cancer patients is feasible with acceptable late toxicity, although the survival remains poor.

**Key Words:** Re-irradiation · Head and neck cancer · Survival · Toxicity

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**Ergebnis nach einer Re-Bestrahlung von Kopf-Hals-Karzinom-Patienten**

**Ziel:** Retrospektive Auswertung von Patienten mit Kopf-Hals-Tumoren nach Re-Bestrahlung.
**Patienten und Methoden:** 51 Patienten mit rezidivierten oder sekundären primären Kopf-Hals-Tumoren erhielten eine Re-Bestrahlung an der Universitätsklinik Leuven (Löwen). Das Überleben und die lokoregionale Kontrolle wurden ermittelt. Die Dosen für die Risiko-Organe wurden den Dosis-Volumen-Histogrammen entnommen. Die mit Re-Bestrahlung verbundenen Toxizitäten wurden ausgewertet.
**Ergebnisse:** Die 2-Jahres-Überlebensrate betrug 30% (Abbildung 2). In einer univariaten Analyse waren eine Operation vor der erneuten Bestrahlung und eine hohe Strahlendosis mit höheren Überlebensraten assoziiert (Tabelle 3). Akuttoxizität Grad 3 oder Spättoxizität Grad 3 und höher traten bei 29.4% bzw. 35.3% der Patienten auf.
**Schlussfolgerung:** Eine Re-Bestrahlung bei Patienten mit Kopf-Hals-Tumoren ist durchführbar mit akzeptabler Spättoxizität; das Gesamt-Überleben ist gering.

**Schlüsselwörter:** Re-Bestrahlung · Kopf-Hals-Tumoren · Gesamt-Überleben · Toxizität oder Nebenwirkungen

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## Introduction

Despite improved tumor control and survival following radiation treatment for head and neck cancer (HNC), through the use of intensified fractionation schedules and the addition of concomitant chemotherapy, locoregional recurrences remain frequent [3, 33, 35, 36, 39, 47]. Currently, long-term disease-free survival in patients with stage III or IV HNC is between 50 and 60% [31, 32]. Locoregional failure is the predominant pattern of failure and the most common cause of death in HNC patients [50]. Moreover, chronic exposure of the upper aerodigestive tract to alcohol and tobacco, the most common risk factors of HNC, is thought to produce field cancerization, a process in which patients are at risk for developing cancer at different mucosal sites. Second primary tumors in the head and neck can occur in up to 30% of patients over 10 years [20, 21, 43].

As most recurrences occur in the first 2 years after primary treatment and 80% arise in previously high-dose irradiated volumes, it is obvious that the management of these recurrences is a challenging clinical problem [4, 6]. The preference in operable patients is salvage surgery with 5-year survival rates ranging from 16–36% [2, 9, 20, 34, 40, 49]. However, due to tumor location and extent, surgery is often irradical with close or positive margins. Moreover, only 20% of patients will be able to undergo salvage surgery because of the extent of the disease, medical contraindications, or patient refusal [20, 22, 49]. Obviously, the risk of morbidity is also higher as a result of radiation-induced tissue changes which complicate healing.

In previously irradiated patients with unresectable recurrent HNC, the standard of care used to be palliative chemotherapy, associated with median survival of 5–9 months and with response rates of between 10 and 40% [11, 12, 20, 54]. Clearly, high-dose re-irradiation in inoperable patients is the only treatment with any potential for cure [7]. Re-irradiation can be delivered using brachytherapy, stereotactic radiosurgery, or external beam radiotherapy with or without chemotherapy and with or without debulking surgery upfront [19]. Evidently, brachytherapy and stereotactic radiosurgery are only options for small-volume disease [2].

Several centers reported encouraging results with aggressive re-irradiation with or without chemotherapy. However, re-irradiation is associated with a high risk of severe complications [7]. It is to be expected that the use of more conformal techniques, such as intensity modulated ration therapy (IMRT), will improve outcome and decrease toxicity of re-irradiation in the head and neck region.

Therefore, we report the outcome of high-dose re-irradiation in HNC patients with the majority of patients treated with three-dimensional (3D) conformal planning techniques or IMRT.

## Materials and Methods

### Patient Characteristics

From 2000–2009, 51 patients with recurrent (n = 37) or second primary (n = 14) HNC received re-irradiation at the University Hospitals Leuven. Two patients had a recurrent tumor and a second primary tumor at the same time. A total of 46 patients (90.2%) were re-irradiated with curative intent, while 5 patients (9.8%) were treated with palliative intent due to low performance status which made them unfit to undergo a radiation treatment (RT) of several weeks**.** There were 45 men and 6 women with a mean age at recurrence of 60 years (range, 42–78 years). The patient characteristics are shown in Table 1.

From the completion of their initial RT, the mean time to retreatment was 60.5 months (range, 3–324 months). A complete history, clinical examination, and computer tomography (CT) scan of the head and neck region were completed in all patients at the time of re-irradiation. Pretreatment workup generally included screening for distant metastases with a chest X-ray, ultrasound of the abdomen, complete blood chemistry, and further imaging, if indicated.

### Treatment

#### *Radiation*

The majority of the patients (n = 48, 94.1%) were re-irradiated using 3D conformal techniques, including 10 patients with IMRT. While 3 patients (5.9%) were re-irradiated using conventional 2D radiation techniques, 1 patient was re-irradiated using external beam RT combined with brachytherapy and another was re-irradiated using RT combined with radiosurgery. All patients had planning CT scans, typically with 3-mm slice spacing and intravenous contrast injection. Patients were immobilized with a thermoplastic 5-point head and neck mask.

Gross tumor volumes (GTV) were outlined and expanded manually by 1.5 cm (range, 0.5–2) to form planning target volumes. All target volumes and adjacent organs at risk were outlined on axial CT slices. The median volumes of clinical (CTV) and planning (PTV) target volumes of recurrence were 63.3 (range, 1.85–230.8) $cm^3$ and 127.2 (range, 25–429.1) $cm^3$, respectively. Beam arrangements and field shapes were designed using 3D beam's eye view (BEV) display targets and normal structures, to avoid re-irradiation of critical normal structures such as the spinal cord and brainstem, while adequately treating the head-and-neck PTV within the 95% isodose.

Treatment planning was performed for all patients using the Eclipse® planning system (Varian Inc, Palo Alto, CA). IMRT was delivered with a sliding window technique and multileaf collimation through a static treatment gantry. Target homogeneity was generally kept within ± 5% of the prescribed dose. Due to disease progression and patient refusal (after 44 and 68 Gy, respectively), 2 patients (3.9%) did not complete their prescribed re-irradiation course. The median radiation dose at retreatment was 60 Gy (range, 37.5–72) at 2 Gy per fraction delivered in 5 fractions weekly. The majority of patients were treated with a 2-Gy fraction (n = 32), 11 with 1.8 Gy per fraction, 1 with combined 2 and 1.8 Gy per fraction,

**Table 1.** Patient characteristics.

**Tabelle 1.** Eigenschaften der Patienten.

| Characteristics | No. of patients | n, % |
|---|---|---|
| Primary tumor site | | |
| Oral cavity | 8 | 15.7% |
| Oropharynx | 9 | 17.6% |
| Larynx | 23 | 45.1% |
| Hypopharynx | 1 | 2% |
| Nasopharynx | 2 | 3.9% |
| Nasal cavity and paranasal sinuses | 4 | 7.8% |
| Lymph nodes of unknown primary | 4 | 7.8% |
| Primary T -classification | | |
| T1 | 13 | 25.5% |
| T2 | 13 | 25.5% |
| T3 | 6 | 11.8% |
| T4 | 13 | 25.5% |
| Tx | 6 | 11.8% |
| Primary N -classification | | |
| N0 | 34 | 66.7% |
| N1 | 3 | 5.9% |
| N2 | 11 | 21.6% |
| N3 | 1 | 2% |
| Nx | 2 | 3.9% |
| Primary tumor histology | | |
| Squamous cell carcinoma | 43 | 84.3% |
| Adenoid cystic carcinoma | 1 | 2% |
| Large cell undifferentiated | 1 | 2% |
| Muco-epidermoid | 1 | 2% |
| Adenocarcinoma intestinal type | 1 | 2% |
| Low grade adnexal tumor | 1 | 2% |
| Sinonasal undifferentiated carcinoma | 1 | 2% |
| Lympho-epithelioma | 1 | 2% |
| Neuro-endocrine | 1 | 2% |
| Primary treatment | | |
| Chemotherapy or targeted therapy | | |
| Yes (concomitant) | 3 | 5.9% |
| Cisplatinum weekly (40 mg/m² ) | 1/3 | |
| Cetuximab weekly (250 mg/m²) | 1/3 | |
| Cisplatinum (100 mg/m², d1)-5-Fluoro-uracil (1000 mg/m², d1–d4) 3 weekly | 1/3 | |
| No | 48 | 94.1% |
| Recurrent tumor site | | |
| Oral cavity | 4 | 7.8% |
| Oropharynx | 14 | 27.5% |
| Larynx | 14 | 27.5% |
| Hypopharynx | 2 | 3.9% |
| Nasopharynx | 3 | 5.9% |
| Nasal cavity and paranasal sinuses | 4 | 7.8% |
| Neck only | 9 | 17.6% |
| Skull base | 1 | 2% |

**Table 1.** (continued)

**Tabelle 1.** (Fortsetzung)

| Characteristics | No. of patients | n, % |
|---|---|---|
| Recurrent tumor pathology | | |
| Squamous cell carcinoma | 39 | 73.6% |
| Adenoid cystic carcinoma | 1 | 1.9% |
| Large cell undifferentiated | 1 | 1.9% |
| Muco-epidermoid | 1 | 1.9% |
| Adenocarcinoma intestinal type | 1 | 1.9% |
| Low grade adnexal tumor | 1 | 1.9% |
| Sinonasal undifferentiated carcinoma | 1 | 1.9% |
| Lympho-epithelioma | 1 | 1.9% |
| Neuro-endocrine | 1 | 1.9% |
| No biopsy | 6 | 11.3% |
| Recurrent T-classification | | |
| T0 | 8 | 15.7% |
| T1 | 2 | 3.9% |
| T2 | 7 | 13.7% |
| T3 | 7 | 13.7% |
| T4 | 18 | 35.3% |
| Tx | 9 | 17.6% |
| Recurrent N-classification | | |
| N0 | 35 | 68.6% |
| N1 | 5 | 9.8% |
| N2: | | |
| N2a (2) | 8 | 15.7% |
| N2b (5) | | |
| N2 (1) | | |
| N3 | 3 | 5.9% |
| Retreatment | | |
| Chemotherapy or targeted therapy | | |
| Yes | 17 | 33.3% |
| Concomitant | 14 | |
| Cisplatinum 3 weekly (100 mg/m²) | 11/14 | |
| Carboplatinum weekly (AUC2) | 1/14 | |
| Cetuximab weekly (250mg/m²) | 1/14 | |
| Carboplatinum(AUC6, d1) 5-Fluorouracil (1000 mg/m²,d1–d4) 3 weekly | 1/14 | |
| Concomitant +induction | 2 | |
| Cisplatinum (100mg/m², d1)-5-Fluoro-uracil (1000 mg/m²,d1–d4) 3 weekly weekly | 2/2 | |
| Induction | 1 | |
| Docetaxel (75 mg/m², d1)-cisplatinum (75 mg/m², d1)-5-Fluorouracil (1000 mg/m²,d1–d4) 3 weekly | 1/1 | |
| No | 34 | 66.7% |

4 with hyperfractionation [31], and 3 with hypofractionation. The mean number of fractions was 30 (range, 13–40). The median radiation dose at initial treatment and the median cumulative delivered radiation dose was 66 (range, 26–72) and 124 Gy (range, 87.5–140), respectively. The median/mean $D_{max}$ spinal cord at primary treatment was 40/32.4 Gy (range, 0–51) and at retreatment was 9/17.8 Gy (range, 0–51.9).

#### *Chemotherapy or Targeted Therapy*

Re-irradiation was delivered with concurrent chemotherapy in 14 patients, while 2 patients also received induction chemotherapy and 1 patient received only induction chemotherapy without concurrent chemotherapy. Chemotherapy regimens at the time of re-irradiation contained either cisplatin (n = 11), cisplatin–5-fluoro-uracil (n = 2), carboplatin–5-fluorouracil (n = 1), carboplatin (n = 1) or docetaxel–cisplatin-5-fluoro-uracil (n = 1). Cetuximab was used in 1 patient.

#### *Surgery*

Fourteen patients (27.5%) with potentially resectable tumors had surgical resection before re-irradiation. Eleven of these 14 patients had microscopic (n = 8) or macroscopic (n = 3) residual disease following surgery, whereas 3 patients had negative surgical margins.

#### *Toxicity*

Acute radiation-related toxicities were classified according to the Common Toxicity Criteria (CTC) system version 3.0. Acute toxicity was assessed weekly during retreatment and monthly for the first 3 months after re-irradiation. It was scored as the highest grade of toxicity during retreatment and 3 months thereafter [55]. Late radiation-related toxicities were classified according to the Radiation Therapy Oncology Group (RTOG)/EORTC morbidity scoring system. Late toxicity was assessed every 3 months starting 6 months after end of retreatment during the first 2 years [56].

### Statistical Analysis

Follow-up was measured from the last day of re-irradiation to the day of death or to the last clinic visit before this analysis (July 2009). The overall (OS), disease-free (DFS), disease-specific survival (DSS), distant control (DC), and locoregional control (LRC) were estimated according to the Kaplan–Meier method. Univariate analysis of the prognostic impact of the following factors on OS, DFS, LRC, DSS, and DC was performed: surgery before re-RT, addition of chemotherapy, time interval between the two radiation treatments (median follow-up of 38 months was used as cut-off, >38 months, ≤38 months), use of IMRT versus 3D conformal RT, re-RT dose (≥60 Gy, <60 Gy), tumor site re-irradiated (nasopharynx or larynx vs. other), second primary versus recurrent cancer, intent of treatment (palliative versus curative) and T-stage at re-irradiation (rT1–3, rT4) . Significance testing was determined using the log-rank test; a p value below 0.05 was considered significant.

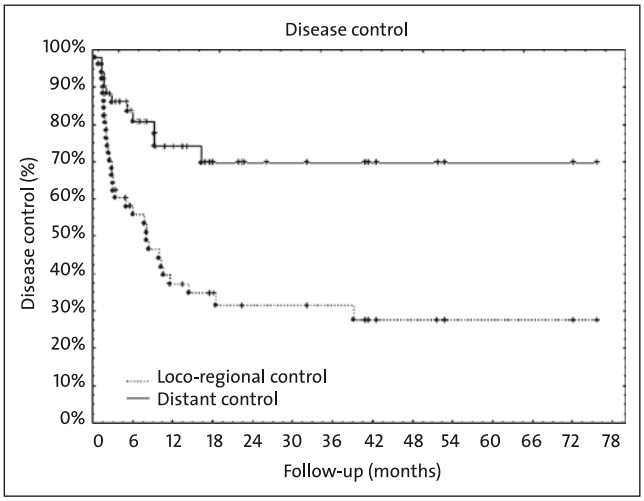


**Figure 1.** Locoregional control and distant control.

**Abbildung 1.** Lokoregionale Kontrolle und Fernmetastasierung.

## Results

From January 2000 to July 2009, a total of 51 patients with recurrent or second primary head and neck cancer received re-irradiation at the Leuven Department of Radiation Oncology. Median follow-up was 9.5 months (range, 1–72.2 months).

### Disease Control

The actuarial estimate of LRC was 32% at 2 years (Figure 1). Of the 51 patients, 33 (64.7%) developed local (n = 11) or locoregional (n = 22) failure during follow-up, with a median time to recurrence of 3.1 months (range, 0.3–39.1 months).

Distant metastases were diagnosed in 12 (23.5%) patients during follow-up after a median of 3.8 months (range, 0.3–16.2 months). The actuarial estimate of disease control was 70% at 2 years (Figure 1). Evaluating failure after re-irradiation, locoregional failure occurred in 13 (39.4%), local failure in 8 (24.2%), locoregional and distant metastasis in 9 (27.3%), local and distant metastasis in 2 (6.0%), and isolated distant failure in 1 (3.0%) patients, respectively. Distant metastasis are reported in the lungs in 5, the bones in 2, the skin in 5, mediastinal (1) and axillary (2) lymph nodes in 3, soft tissues, the liver, and the spleen in 1 patient each.

### Survival

The actuarial estimate of overall survival (OS) was 30% at 2 years (Figure 2). The median survival following completion of re-irradiation was 9.53 months (range, 0.9–72.2 months). The median survival of patients with curative intent vs. palliative intent was 10.3 months and 5 months, respectively.

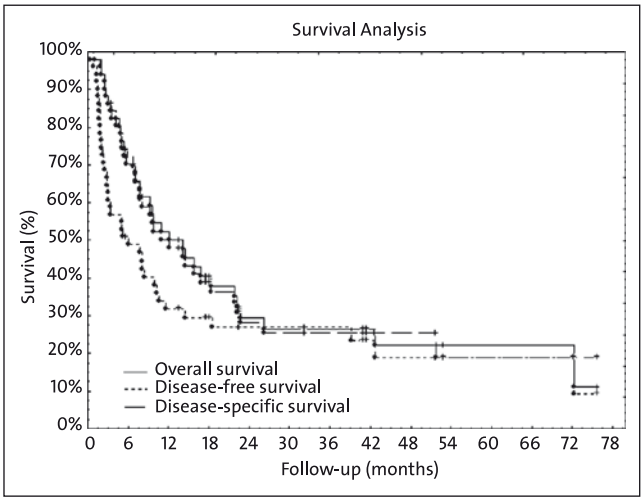


**Figure 2.** Overall survival, disease-free, and disease-specific survival for all patients.

**Abbildung 2.** Gesamtüberleben, krankheitsfreies und krankheitsspezifisches Überleben für alle Patienten.

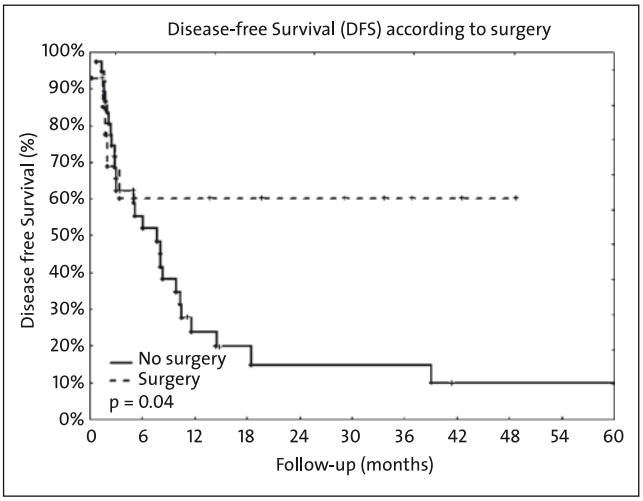


**Figure 3.** Disease-free survival according to surgery.

**Abbildung 3.** Krankheitsfreies Überleben nach Operation.

A total of 34 patients (66.7%) died during follow-up after a median of 7.6 months (range, 0.9–72.2 months): 31 patients (93.9%) died due to disease and 3 patients (8.8%) died of another cause. The DSS rate was 28% at 2 years (Figure 2). 12 patients (23.5%) were still alive and disease free after a median interval of 27.4 months (range, 5.4–75.8 months). The actuarial disease-free survival (DFS) rate was 27.5% at 2 years (Figure 2).

### Toxicity

Acute and late toxicity was assessed retrospectively by documenting all symptoms recorded during and following re-irradiation (Table 2). Grade 3 acute toxicity occurred in 15 patients (29.4%): dysphagia in 10, mucositis in 8, and skin toxicity in 3 patients. No grade 4 acute toxicity was reported. Grade 3 or 4 late toxicity occurred in 18 patients (35.3%). Optic nerve neuropathy, brain necrosis, and osteoradionecrosis occurred in 1 patient each 2.5, 6, and 16 months, respectively, after re-irradiation. There were no incidences of carotid rupture in our series. Fistula formation was reported in 5 of 17 patients with severe dysphagia. Gastrostomy tube dependence ≥6 months after re-irradiation was reported in 11 patients (21.6%).

### Univariate Analysis of Prognostic Factors

Univariate analysis of potential prognostic factors found that a tumor site other than nasopharynx and larynx was significantly associated with improved locoregional control (LRC), disease-specific survival (DSS), and disease-free survival (DFS). Surgery before re-irradiation was also significantly associated with improved DFS (Figure 3) and showed a trend for improved LRC and DSS (Table 3). The 2-year DFS was 60% in the surgery group vs. 14% in the nonsurgery group ($p = 0.04$). Also a high re-irradiation dose was significantly associated with improved DSS (Table 3, Figure 4). Palliative intent showed a trend for decreased survival (Table 3). T4-stage at re-irradiation showed a trend for decreased LRC (Table 3, Figure 5). Addition of chemotherapy, second primary versus recurrence, time interval between two radiation treatments,

**Table 2.** Different grades of acute and late toxicity during and after re-irradiation.

**Tabelle 2.** Verschiedene Grade der akuten und späten Toxizität während und nach der Re-Bestrahlung.

| | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|---|
| **Acute toxicity** | | | | | | |
| Skin | 0 (0%) | 13 (25.5%) | 35 (68.6%) | 3 (5.9%) | 0 (0%) | 0 (0%) |
| Mucosa | 0 (0%) | 9 (17.6%) | 34 (66.7%) | 8 (15.7%) | 0 (0%) | 0 (0%) |
| Dysphagia | 0 (0%) | 9 (17.6%) | 32 (62.7%) | 10 (19.6%) | 0 (0%) | 0 (0%) |
| **Late toxicity** | | | | | | |
| Skin | 0 (0%) | 0 (0%) | 49 (96.1%) | 2 (3.9%) | 0 (0%) | 0 (0%) |
| Mucosa | 0 (0%) | 7 (13.7%) | 41 (80.4%) | 0 (0%) | 3 (5.9%) | 0 (0%) |
| Esophagus | 0 (0%) | 2 (3.9%) | 32 (62.7%) | 12 (23.5%) | 5 (9.8%) | 0 (0%) |
| Subcutaneous tissue | 0 (0%) | 0 (0%) | 39 (76.5%) | 12 (23.5%) | 0 (0%) | 0 (0%) |

and RT technique were not predictive for LRC, OS, DFS, or DSS.

## Discussion

The results of this study demonstrate that re-irradiation is a feasible option in previously irradiated HNC patients. As mentioned above, the treatment options for these patients are limited. A review of data from the available literature is shown in Table 4**.** It should be noted that 5-year survival rates range from as low as 13% in unselected patients to as high as 93% in selected patients [20]. Long-term survival after re-irradiation ranged between 13 and 20%, while local or regional control ranged from 13–33% [10, 14, 37, 46]. Our results are similar to previous studies showing overall survival rates of 50%, 30%, and 22.5% at 1, 2, and 5 years, respectively (Table 4).

In the literature, several prognostic factors have been identified in patients receiving re-irradiation [7, 20]. First, debulking surgery before re-irradiation results in better outcomes [7, 9, 20]. Our results show 2-year DFS of 60% in the surgery group vs. 14% in the nonsurgery group. In our study, patients who are treated with both surgery and radiotherapy had a better prognosis. This is probably due to the fact that patients for whom operation is feasible are patients with smaller recurrent tumors with an inherent better prognosis.

Second, some authors documented better outcomes in some re-irradiated anatomic sites such as laryngeal [51] and nasopharyngeal cancer [7, 27, 52]. Our results show, however, no better results in DFS and LRC in re-irradiation of recurrent laryngeal and nasopharyngeal cancer than other tumor sites [7, 27, 51, 52]. If the laryngeal recurrences in our study are considered, it can be seen that the most were stoma relapses that received no surgery before re-irradiation. This is in contrast with the literature where the majority of patients re-irradiated at the larynx were treated with surgery first or had early stage laryngeal recurrences [7, 51]. In case of nasopharyngeal cancer, most of recurrences in the literature were in an early stage and were re-irradiated with brachytherapy

**Table 3.** Univariate analysis of predictors for overall survival, disease-free survival, disease-specific survival, and locoregional control.

**Tabelle 3.** Univariate Analyse von Prädiktoren für Gesamtüberleben, krankheitsrfeies Überleben, krankheitsspezifisches Überleben und lokoregionale Kontrolle.

| | | OS | DFS | DSS | LRR |
|---|---|---|---|---|---|
| **Variable** | **n** | **p value** | **p value** | **p value** | **p value** |
| Tumor site | | 0.11 | **0.04** | **0.03** | **0.02** |
| nasopharynx/larynx | 17 | | | | |
| vs. other | 34 | | | | |
| Intent of treatment | | 0.06 | 0.52 | 0.15 | 0.46 |
| curative | 46 | | | | |
| vs. palliative | 5 | | | | |
| Re-irradiation dose | | 0.07 | 0.08 | **0.05** | 0.10 |
| ≥60 | 32 | | | | |
| vs. <60 | 19 | | | | |
| Surgery before re-RT | | 0.12 | **0.04** | 0.09 | 0.09 |
| yes | 14 | | | | |
| vs. no | 37 | | | | |
| Tumor stage at re-irradiation | | 0.83 | 0.89 | 0.69 | 0.38 |
| rT1–T3 | 16 | | | | |
| rT4 | 18 | | | | |

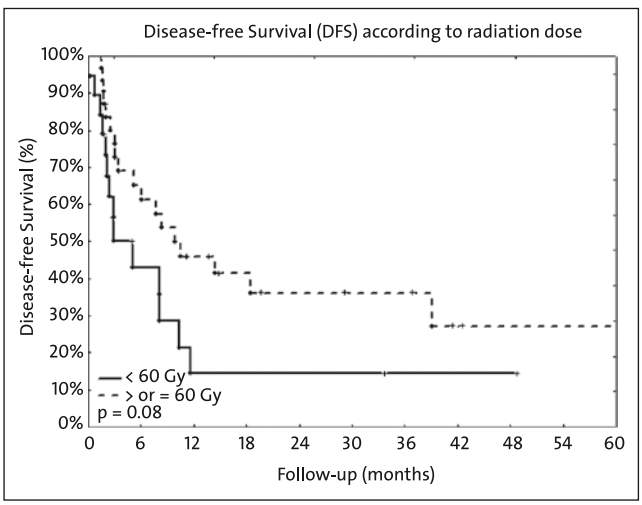


**Figure 4.** Disease-free survival according to radiation dose.

**Abbildung 4.** Krankheitsfreies Überleben nach Strahlendosis.

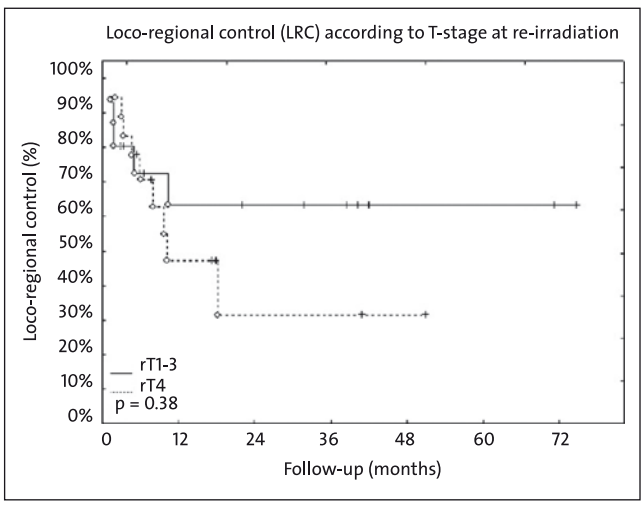


**Figure 5.** Locoregional control according to T-stage at re-irradiation.

**Abbildung 5.** Lokoregionale Kontrolle nach T-Stadium bei Re-Bestrahlung.

**Table 4.** Review of literature. n: number of patients; (C)RT: (chemo)radiotherapy; IMRT: intensity modulated radiotherapy; NS: not specified.
**Tabelle 4.** Literaturstudie.

| References | n | Treatment | Time point (years) | Local control (%) | Overall survival (%) | Severe late complication rate (%) |
|---|---|---|---|---|---|---|
| De Crevoisier [9] | 25 | surgery+CRT 60 Gy | 2 | NS | 43 | 16–40 |
| Dawson [7] | 40 | (C)RT 60 Gy | 2 | 19.5 | 32.6 | 18 |
| Stevens [46] | 100 | RT 50 Gy | 5 | 27–60 | 17–37 | 9 |
| Haraf [16] | 45 | CRT 50–58 Gy | 2 | 26 | 22 | 11 |
| | | | 5 | 20 | 14.6 | |
| Wang [51] | 20 | RT 60–70 Gy | 5 | 60 | 93 | – |
| Biagioli [2] | 41 | CRT(IMRT)60 Gy | 2 | NS | 48.7 | 14.6 |
| Salama [41] | 115 | CRT 58 Gy | 3 | 51 | 22 | 16 |
| De Crevoisier [8] | 169 | (C)RT 60–65 Gy | 2 | NS | 21 | 8–41 |
| | | | 5 | | 9 | |
| Schaefer [42] | 32 | CRT 60 Gy | 2 | 31 | 5 | 9.4 |
| Lee [26] | 105 | (C)RT 59.4 Gy, 70% IMRT | 2 | 42 | 37 | 11 |
| Popovtzer [38] | 66 | (C)RT 68 Gy | 2 | 27 | 40 | 29 |
| | | | 5 | 19 | | |
| Hehr [17] | 27 | CRT 40 Gy | 3 | NS | 18 | – |
| Langendijk [23] | 34 | RT 60–66 Gy | 2 | 27 | 28 | 3–24 |
| Kasperts [21] | 39 | Surgery+RT 60–66 Gy | 3 | 74 | 44 | 36 |
| Emami [10] | 48 | Surgery+RT | 5 | 20.8 | 20 | 16 |
| | 40 | RT | 5 | 13 | 13 | |
| Sulman [48] | 74 | RT(IMRT) 60 Gy | 2 | 64 | 58 | 20 |
| Spencer [44] | 81 | CRT 60 Gy | 1 | NS | 41.7 | 24 |
| | | | 2 | | 16.2 | |
| Weppelmann [53] | 21 | CRT 40–48 | 1 | NS | 56 | – |
| Goldstein [15] | 41 | RT 60–70 Gy | 1 | NS | 39 | 53.8–75 |
| Nagar [29] | 29 | CRT 34 Gy | 1 | NS | 41 | 14 |
| Machtay [28] | 16 | Surgery+ CRT 54–66 Gy +amifostine | 3 | 81 | 63 | 38 |
| Pomp [37] | 55 | (C)RT 46 Gy | 5 | 33 | 20 | – |
| Langer [24] | 99 | CRT 60 Gy | 1 | NS | 50.2 | 32 |
| | | | 2 | | 25.9 | |
| Chua [5] | 31 | RT(IMRT) 54 Gy | 1 | 56 | 63 | 19–25 |
| Platteaux | 51 | (Surgery) + (C)RT 60 Gy | 2 | 32 | 30 | 35.3 |

with or without external beam radiotherapy, which results in better outcomes in contrast with our patients [5, 7, 52].

Third, second primary cancers have better survival and local control rates than recurrent cancers due to aggressiveness and radiation resistance of the recurrent tumor cell population [44, 46]. Our results did not show any statistically significant difference in outcomes, probably due to the limited number of second primaries in this analysis.

Fourth, some authors suggest that the longer the time interval since prior irradiation, the better the survival and local control is [44, 45]. However, our results show no statistical significant difference in outcomes, which is in agreement with others [13].

Fifth, higher radiation doses results in better LRC and survival [10, 16]. Our data show that higher radiation doses are a prognostic factor in re-irradiated tumors. The argument, therefore, lies in the hypothesis that recurrent tumor cell populations have risen from radiation-resistant clonogens [16, 25, 46]. It must also be noted that patients selected for higher radiation doses are mostly in a relatively good general condition with an inherently better prognosis.

Sixth, addition of concomitant chemotherapy may represent an effective approach due to radiation sensitization and direct cytotoxicity [16, 18, 20]. Our results, however, did not show any statistically significant difference in outcomes, again probably due to the limited number of patients which hampered our ability to detect small differences.

It is evident that from our nonrandomized data we cannot draw firm conclusions about the value of operation and high radiation doses on the outcome. However, randomized trials on re-irradiation have not been carried out and are unlikely to be.

Unacceptable normal tissue toxicity can be a matter of concern in re-irradiated patients due to high cumulative

radiation doses [1, 20]. Normal tissue tolerance data are scarce, but some authors suggested that cumulative biologically equivalent doses of up to 130 Gy in 2 Gy are safe [20, 30]. The prevalence and the severity of complications depend on the modality of radiation, the site irradiated, the time interval between the radiation treatments, and the rate of long-term survival. Complication rates vary from 7–50% but are higher for re-irradiation of the nasopharynx due to its proximity to brain, cranial nerves, and the visual system [8, 9, 15, 18, 20, 26]. Our results are in agreement with results from the literature. The reporting of late toxicity is particularly challenging in this population, which is likely to harbor high rates of cumulative effects from multiple therapies. Accurate estimation of late injury is moreover difficult because of the small numbers of survivors.

Lowering the complications can perhaps be strived for by using newer radiation techniques, e.g., IMRT, enabling us to limit the volume of normal tissue irradiated, while limiting the CTV to the high risk area or GTV with some margin [22]. The use of cytoprotective agents such as amifostine should also be investigated in future trials [22].

## Conclusion

Our results suggest that high-dose re-irradiation is a possible and potentially curative approach for recurrent or second primary HNC with an acceptable toxicity. A careful selection of patients should be made. Further improvements of radiation techniques and novel treatment strategies to improve outcome and to minimize toxicity in patients with HNC requiring re-irradiation are warranted.

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