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Original Research Article

# Incidence of contralateral regional failure in the electively irradiated contralateral neck of patients with head and neck squamous cell carcinoma

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ABSTRACT

*Background:* The vast majority of patients with head and neck squamous cell carcinoma (HNSCC) routinely undergo elective nodal irradiation (ENI) to both sides of the neck. Little is known about the extent to which bilateral ENI prevents regional failure (RF) and contralateral RF (cRF) in particular, while such knowledge is necessary to evaluate the results of more selective approaches like unilateral ENI. We investigated the rate and pattern of RF after bilateral ENI, the rate of cRF in the electively irradiated contralateral neck, and tried to identify risk factors for development of cRF.

*Materials and methods:* Retrospective cohort study of a consecutive series of 605 patients with T1-4N0-3 HNSCC treated between 2008 and 2017 with primary (chemo)radiation and bilateral ENI.

*Results:* Median follow-up was 43 months (range 1.4–126). Three-year cumulative incidence of RF was 12.7%. Three-year cumulative incidences of ipsilateral RF (iRF) and cRF were 10.6% and 2.8%, respectively. All cRF occurred within the electively treated volume. Salvage treatment was possible in 65% and 59% of patients with iRF and cRF, respectively ($p = 0.746$). The 3-year overall survival rates after RF in patients with iRF and cRF were 27.4% and 41.2%, respectively ($p = 0.713$). Three-year cancer-specific survival rates were 31.6% and 48.1%, respectively ($p = 0.634$). In multivariate analysis, no significant predictive factors were identified for cRF after bilateral ENI.

*Conclusion:* Contralateral regional failure is rare, but still occurs in 2.8% of patients treated with bilateral ENI. The possibilities for salvage treatment, the rates of overall survival and cancer-specific survival were comparable to patients with iRF.



## 1. Introduction

The concept of elective nodal irradiation (ENI) was introduced in the sixties by Fletcher [1] and supported later on by others [2,3]. Since then, bilateral ENI has been the standard treatment for the vast majority of head and neck squamous cell carcinoma (HNSCC) patients (with the exception of early stage glottic laryngeal tumors and very lateralized tonsillar fossa tumors). In recent decades imaging techniques have become more accurate and reliable, arguably resulting in a smaller occult tumor load in clinically negative lymph nodes. Despite this, the paradigm of bilateral ENI remains unchanged out of concern for regional failure (RF), and specifically contralateral regional failure (cRF). Though ENI has shown to significantly improve regional control and overall survival (OS) [4–6], the extent to which it will prevent the occurrence of RF, specifically at the contralateral side, is not clear. Meanwhile,

*Abbreviations:* cRF, contralateral regional failure; CSS, cancer specific survival; CTV, clinical target volume; DM, distant metastasis; ENI, elective nodal irradiation; GTV, gross tumor volume; HNSCC, head and neck squamous cell carcinoma; HPV, human papilloma virus; IMRT, intensity modulated radiotherapy; iRF, ipsilateral regional failure; LF, local failure; OPC, oropharyngeal cancer; OS, overall survival; PTV, planning target volume; RF, regional failure; VMAT, volumetric arc therapy.

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there is growing evidence that the incidence of cRF in well-selected HNSCC after unilateral ENI is very low [7,8].

Bilateral ENI, large treated volumes and chemoradiation are important predictors for radiation-induced toxicity [9–13]. As a consequence of improved prognosis, and, among young patients, the increased incidence of human papilloma virus (HPV)-associated oropharyngeal cancer (OPC), patients will live longer with the burden of permanent radiation sequelae. Therefore, there is an increasing need for selection tools to expand the indications for unilateral ENI. To be able to fairly compare the results of more selective approaches to those of bilateral ENI, more insight in the incidence of RF and cRF and their spatial relationship to the treatment volume is needed. Notably, data on the incidence of RF in the electively treated neck is scarce. In the few published reports, the incidence of RF in electively irradiated lymph node regions varied between 1 and 11% [14–19]. However, none of these studies mentioned the exact incidence of cRF in the electively irradiated contralateral neck.

The aim of the current study was to investigate the rate and the pattern of RF after bilateral ENI, to investigate the rate of cRF in the electively irradiated contralateral neck, and to identify possible risk factors for RF and specifically for cRF.

## 2. Materials and methods

### 2.1. Study population

Seven hundred and three consecutive patients with histologically proven primary HNSCC of the oropharynx, larynx and hypopharynx, treated in our institution with (chemo)radiation with curative intent between January 2008 and January 2017, were identified in our database. Ninety-eight patients were excluded because they were either electively irradiated to one side of the neck (n = 25) or they had T1 glottic laryngeal cancer and received no elective nodal irradiation (n = 73), leaving 605 patients who were electively irradiated to both sides of the neck and are the sub-

**Table 1**
Patient demographics for all patients; and for patients with iRF and cRF.

| | All patients (n = 605) | | iRF (n = 54) | | cRF (n = 17) | |
|---|---|---|---|---|---|---|
| | N | (%) | N | (%**) | N | (%**) |
| Age (years) | | | | | | |
| Median | 63 | | 63 | | 61 | |
| Range | 36–88 | | 43–83 | | 49–81 | |
| Gender | | | | | | |
| Male | 429 | (71%) | 47 | (11.0%) | 13 | (3.0%) |
| Female | 176 | (29%) | 7 | (4.0%) | 4 | (2.3%) |
| Smoking | | | | | | |
| Current smokers | 457 | (76%) | 42 | (9.2%) | 15 | (3.3%) |
| Former smokers | 69 | (11%) | 5 | (7.2%) | 2 | (2.9%) |
| Nonsmokers | 79 | (13%) | 7 | (8.9%) | 0 | (0.0%) |
| Tumor site | | | | | | |
| Oropharynx | 284 | (47%) | 24 | (8.5%) | 7 | (2.5%) |
| Hypopharynx | 97 | (16%) | 12 | (12.4%) | 3 | (3.1%) |
| Larynx | 224 | (37%) | 18 | (8.0%) | 7 | (3.1%) |
| HPV status in OPC | | | | | | |
| Positive | 122 | (43%) | 7 | (5.7%) | 1 | (0.8%) |
| Negative | 129 | (45%) | 16 | (12.4%) | 5 | (3.9%) |
| Unknown | 33 | (12%) | 1 | (3.0%) | 1 | (3.0%) |
| T-classification* | | | | | | |
| T1 + T2 | 338 | (56%) | 25 | (7.4%) | 10 | (3.0%) |
| T3 + T4 | 267 | (44%) | 29 | (10.9%) | 7 | (2.6%) |
| Relation of PT to the midline | | | | | | |
| Lateralized | 297 | (49%) | 35 | (11.8%) | 8 | (2.7%) |
| At or crossed the midline | 308 | (51%) | 19 | (6.2%) | 9 | (2.9%) |
| N-classification* | | | | | | |
| N0 | 235 | (39%) | 7 | (3.0%) | 6 | (2.6%) |
| N1 | 70 | (12%) | 6 | (8.6%) | 2 | (2.9%) |
| N2a-b | 188 | (31%) | 24 | (12.8%) | 9 | (4.8%) |
| N2c | 97 | (16%) | 14 | (14.4%) | 0 | (0.0%) |
| N3 | 15 | (2%) | 3 | (20.0%) | 0 | (0.0%) |
| Extra-capsular extension | | | | | | |
| Yes | 89 | (24%) | 39 | (43.8%) | 4 | (4.5%) |
| No | 281 | (76%) | 15 | (5.3%) | 13 | (4.6%) |
| Nodal volume (cc) | | | | | | |
| Median | 10.7 | | 15.5 | | 14.7 | |
| Range | 0.3–194.1 | | 0.9–96.2 | | 1.8–110.2 | |
| Nodal number | | | | | | |
| Median | 2 | | 2 | | 2 | |
| Range | 1 to 13 | | 1 to 12 | | 1 to 3 | |
| Neck levels involved | (cN + ) | | (As location of failure) | | | |
| Level I | 30 | | 3 | | 0 | |
| Level II | 330 | | 45 | | 11 | |
| Level III | 228 | | 31 | | 9 | |
| Level IV | 74 | | 13 | | 1 | |
| Level V | 30 | | 6 | | 1 | |
| Level VI | 4 | | 1 | | 0 | |
| Retropharyngeal space | 48 | | 6 | | 1 | |

Abbreviations: iRF: ispilateral regional failure; cRF: contralateral regional failure; HPV: human papilloma virus; OPC: oropharyngeal cancer; PT: primary tumor.
* TNM-classification according to AJCC staging manual, 7th edition.
** % of total number of patients with this baseline characteristic.

ject of the current analysis. The local institutional review board waived informed consent for the retrospective analyses of clinical data (METC18.0690).

### 2.2. Pre-treatment evaluation

Pre-treatment evaluations consisted of complete history and physical examination, including diagnostic panendoscopy under general anesthesia. For staging, all patients underwent a chest X-ray, bilateral neck ultrasound with fine needle aspiration cytology if suspected to be positive, and head and neck MRI or CT scan. In patients with locally-advanced disease (T3/4,N2c/N3), 18-FDG-PET/CT was also performed. For staging, the 7th edition of the American Joint Committee on Cancer (AJCC) staging manual was used.

### 2.3. (Chemo)radiotherapy

Patients were immobilized in supine treatment position in a custom-made head-and-neck mask. For planning, contrast-enhanced CT-scan simulation was performed. The gross tumor volume (GTV) of the primary tumor and the involved node(s) were delineated. The clinical target volume ($CTV_{70Gy}$) was generated by adding 1 cm margin to the delineated GTV, using volumetric expansion and subsequently edited to the adjacent non-involved bone and/or air. All patients were electively irradiated to both sides of the neck. The elective $CTV_{46Gy}$ of the neck for all tumor sites was defined as level I-V in case of node-positive and level II-IV in case of node-negative neck. Retropharyngeal spaces were electively treated in patients with tumors invading the posterior wall of the pharynx or the postcricoid region. Level IB was irradiated only in cases of involvement of the oral cavity. Level VI was electively irradiated in case of transglottic laryngeal cancer, glottic laryngeal cancer with subglottic extension and in case of postcricoid carcinoma. The elective neck levels were delineated according to the European Organization for Research and Treatment of Cancer (EORTC) consensus guidelines [20,21]. The planning target volume (PTV) included a margin of 5 mm beyond the CTVs. Since April 2015, a 3 mm margin was used to expand the CTV to the PTV. The radiation dose consists of 70 Gy to the high-risk PTV, given in 2 Gy per fraction, 6 fractions a week in case of radiotherapy alone and 5 fractions a week in case of chemoradiation; and elective irradiation of the neck to a dose 46 Gy in 23 fractions in case of sequential boost and to 54.25 Gy in 35 fractions in case of concomitant boost. All patients were treated with intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT). Set-up verification and correction of the patients was done by means of an online correction protocol using daily cone-beam CT. Concomitant cisplatin (100 mg/m$^2$ in the 1st, 4th and 7th week of treatment) was added to the radiotherapy in case of locally advanced oropharyngeal and laryngeal cancer (T3/4, N2c/N3), or extracapsular extension (as determined by CT or MRI). In hypopharyngeal cancer, cisplatin was added in all node-positive disease, regardless of T-stage. Patient who were unfit for cisplatin received weekly cetuximab.

### 2.4. Follow-up

During treatment patients were seen twice weekly at the outpatients clinic in order to monitor the acute toxicity. After completion of treatment, patients were seen every 2 weeks until the acute radiation-induced toxicity had subsided. Response evaluation was performed three months after treatment by neck ultrasound and either CT or MRI. Thereafter, patients were seen 3-monthly for the first year, 4-monthly for the second year and 6-monthly thereafter. At each visit, history and clinical examination were performed, including flexible laryngoscopy when indicated.

### 2.5. End points

The primary end points of the current study were the incidence of RF, the incidence of RF in the electively irradiated neck, and specifically the incidence of cRF in electively irradiated contralateral neck. Secondary end points were rates of local failure (LF), distant metastasis (DM), OS and cancer-specific survival (CSS).

### 2.6. Patterns of regional failure

Besides subdividing RF into ipsilateral RF (iRF) and cRF, the regional recurrences were classified into 4 subgroups in relation to the received dose of radiotherapy at the region of RF:

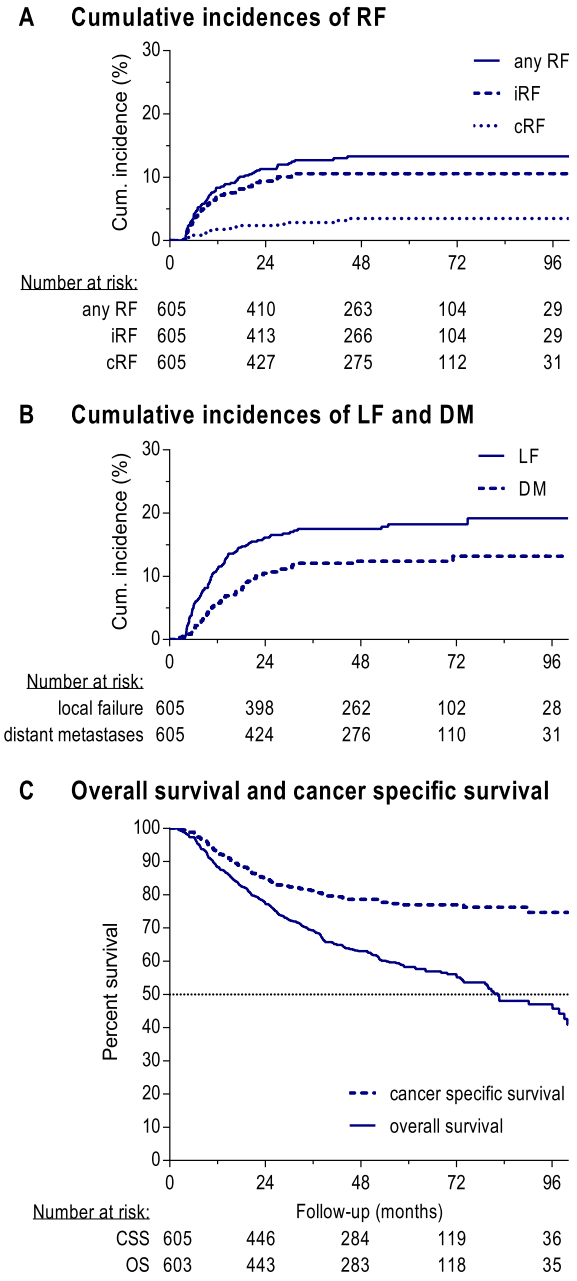


**Fig. 1.** Cumulative incidences of regional failure and survival. Cumulative incidences are shown for any RF, iRF and cRF (A); for LF and DM (B); and for OS and CSS (C). *Abbreviations*: RF: regional failure; iRF: ipsilateral regional failure; cRF: contralateral regional failure; LF: local failure; DM: distant metastasis; OS: overall survival; CSS: cancer specific survival.

(1) RF within the boost volume: when the recurrence occurs in the 70 Gy region
(2) RF in the intermediate-dose level: when the recurrence occurs in a region received between 46 and 70 Gy, or
(3) RF in the electively treated volume: when the recurrence occurs in a neck level that received the elective dose of 46 Gy
(4) RF outside the elective and boost volumes: when the recurrence occurs in a region received no radiation dose.

### 2.7. Statistical analysis

The cumulative incidence of LF, RF, DM, OS, and CSS were estimated from the start of (chemo)radiation using the Kaplan-Meier method. In the analysis of LF, RF, and DM, patients with events other than the event of interest, or with no event at last follow-up, were censored. For OS, death from any cause was considered an event. For CSS, only death from cancer was considered an event. In both cases, all other patients were censored. The log-rank test was used to assess differences between groups. Additionally, OS was compared between patients with iRF and cRF counting from the date of iRF and cRF respectively (i.e., a landmark analysis). Cox proportional hazards regression was used for uni- and multivariable analysis. Characteristics of patients with iRF and cRF were compared using Mann-Whitney-U tests, Fischer's exact test and chi-square tests, conditionally on experiencing a RF (i.e., within the subgroup of patients with an iRF or a cRF). Patients with bilateral RF were counted in the cRF group. Statistical analysis was performed in SPSS version 22. All tests were two-sided with an assumed significance level of $p < 0.05$, save the threshold for inclusion in the multivariate Cox regression model ($p < 0.2$).

## 3. Results

Patient baseline characteristics of the entire group, and of those who developed iRF or cRF, are shown in Table 1. Median follow-up was 43 months (range 1.4–126). Three patients were lost to follow-up after 27, 28 and 110 months, respectively, without evidence of recurrent disease. Of the entire group (n = 605), 71 patients (11.7%) developed RF; 17 were cRF (2.8%), of which 3 were bilateral RF (0.5%); and 54 (8.9%) were solely iRF. For further analysis, bilateral RF was grouped with cRF. The 3-year cumulative incidence of RF on any side was 12.7% (95% CI, 7.3–19.7), consisting of 10.6% (95% CI, 5.4–17.7) for iRF and 2.8% (95% CI, 0.3–11.8) for cRF ($p < 0.001$) (Fig. 1). Median time to detection was 9.0 months (range 3.5–31.2) for all RF, and 7.7 and 9.6 months for iRF and cRF, respectively ($p = 0.284$). In the multivariable analysis of risk factors for the development of RF, only N-stage and HPV-status were significantly associated with RF (Table 2). For cRF, no significant predictors were found.

RF developed within an electively treated neck level in 26 patients (4.3%), with a 3-year cumulative incidence of 4.5% (95% CI, 1.0–12.6). Regarding the relation of the 71 RFs to the received dose of radiation, RF developed within the high dose (boost) volume in 40 patients (56.3% of all RFs), within the elective volume in 26 patients (36.6%), within the intermediate-dose volume in 4 patients (5.7%), and outside the elective and boost volumes in the retropharyngeal space in one patient (1.4%). All 17 cRFs developed in the electively treated volume.

RF occurred simultaneously with LF in 31 patients (44%), and isolated in 40 patients (56%). In patients with iRF and cRF, isolated RF was reported in 58% and 47% of cases, respectively ($p = 0.430$). Salvage treatment was possible in 45 patients with RF (63%), 44

**Table 2**
Cox regression analysis of risk factors for RF, cRF and death from any cause.

| Regional failure | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | p-value | HR | 95%CI | p-value |
| Age (ref: <65 years) | 1.37 | 0.80–2.37 | 0.254 | | | |
| Smoking status (ref: non-smoker) | 1.38 | 0.77–2.47 | 0.282 | | | |
| T-stage (ref: T1/T2) | 1.46 | 0.92–2.33 | 0.109 | 1.04 | 0.64–1.68 | 0.887 |
| N-stage (ref: N0) | 3.09 | 1.69–5.63 | **<0.001** | 3.72 | 1.99–6.95 | **<0.001** |
| Tumorsite (ref: HPV-negative oropharynx) | | | | | | |
| HPV-positive oropharynx | 0.35 | 0.15–0.79 | **0.011** | 0.31 | 0.13–0.73 | **0.007** |
| Larynx | 0.65 | 0.36–1.16 | 0.142 | 1.03 | 0.56–1.90 | 0.916 |
| Hypopharynx | 1.04 | 0.54–2.02 | 0.911 | 0.96 | 0.49–1.89 | 0.909 |
| **Contralateral regional failure** | **Univariate analysis** | | | **Multivariate analysis** | | |
| | HR | 95%CI | p-value | HR | 95%CI | p-value |
| Age (ref: <65 years) | 0.95 | 0.27–3.29 | 0.930 | | | |
| Smoking status (ref: non-smoker) | 2.62 | 0.60–11.47 | 0.200 | | | |
| T-stage (ref: T1/T2) | 1.00 | 0.38–2.64 | 0.997 | | | |
| N-stage (ref: N0) | 1.26 | 0.46–3.40 | 0.653 | | | |
| Tumorsite (ref: HPV-negative oropharynx) | | | | | | |
| HPV-positive oropharynx | 0.17 | 0.02–1.47 | 0.108 | | | |
| Larynx | 0.73 | 0.23–2.30 | 0.594 | | | |
| Hypopharynx | 0.83 | 0.20–3.50 | 0.800 | | | |
| Relation PT to midline (ref: no midline involvement) | 1.17 | 0.45–3.04 | 0.744 | | | |
| **Death from any cause** | **Univariate analysis** | | | **Multivariate analysis** | | |
| | HR | 95%CI | p-value | HR | 95%CI | p-value |
| Age (ref: <65 years) | 1.49 | 1.17–1.90 | **0.001** | 1.49 | 1.16–1.92 | **0.002** |
| Smoking status (ref: non-smoker) | 2.09 | 1.41–2.95 | **<0.001** | 1.62 | 1.14–2.30 | **0.008** |
| T-stage (ref: T1/T2) | 1.66 | 1.30–2.13 | **<0.001** | 1.30 | 1.00–1.69 | 0.050 |
| N-stage (ref: N0) | 1.44 | 1.11–1.86 | **0.006** | 1.67 | 1.24–2.25 | **0.001** |
| Tumorsite (ref: HPV-negative oropharynx) | | | | | | |
| HPV-positive oropharynx | 0.16 | 0.09–0.28 | **<0.001** | 0.19 | 0.10–0.34 | **<0.001** |
| Larynx | 0.68 | 0.50–0.93 | **0.015** | 0.90 | 0.64–1.25 | 0.511 |
| Hypopharynx | 1.32 | 0.94–1.85 | 0.106 | 1.40 | 1.00–1.96 | 0.053 |

*Abbreviations*: RF: regional failure; cRF: contralateral regional failure; ref: reference category; HPV: human papilloma virus; PT: primary tumor; HR: hazard ratio; 95%CI: 95% confidence interval.

by means of neck dissection and in one patient by means of chemoradiation to the RF in the retropharyngeal space. Thirty-five patients with iRF (65%) and 10 patients with cRF (59%) were successfully salvaged (p = 0.746, $\chi^2$). In 26 patients, no salvage treatment was given, due to irresectability of either the local or regional recurrence. At the time of the analysis, 19 patients with RF were still alive (27%); 5 patients with cRF (29%), and 14 with iRF (26%). The 3-year OS rates after RF in patients with iRF and cRF were 27.4% and 41.2%, respectively (p = 0.713). Three-year CSS rates after RF were 31.6% and 48.1%, respectively (p = 0.634) (Fig. 2). Similarly, no difference in OS was observed between patients with iRF and cRF in the group with isolated RF (n = 25, p = 0.573, data not shown) and in the group where RF occurred simultaneously with LF, DM, or both (n = 46, p = 0.265, data not shown). Cox regression analysis showed that only salvage treatment and HPV-status were significantly associated with OS after RF (Table 3).

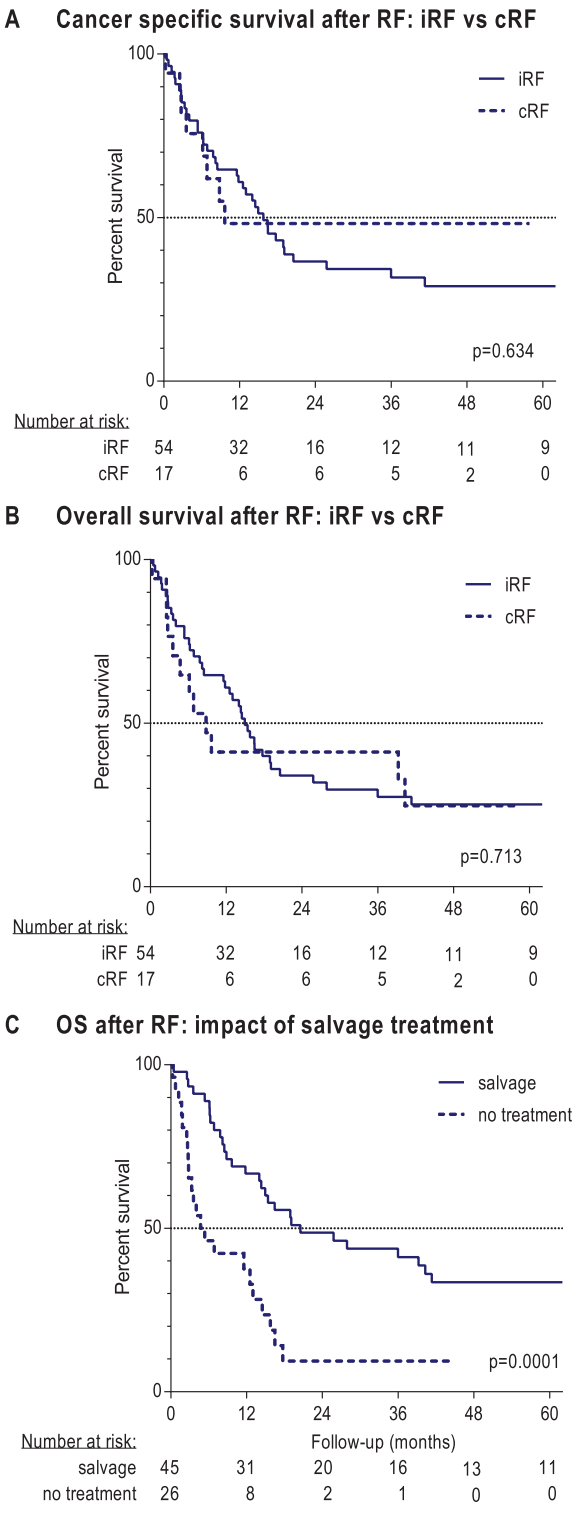


**Fig. 2.** Survival after regional failure. For patients with RF (n = 71), CSS (A) and OS (B) are shown from the moment of RF. For the same group, OS from the moment of RF is shown for patients with or without salvage treatment (C). *Abbreviations*: RF: regional failure; CSS: cancer specific survival; OS: overall survival.

For the entire group, median OS was 82.4 months. The 3-year cumulative incidence of LF and DM were 17.5% and 12.1%, respectively and 3-year cumulative incidence of OS and CSS were 69.3% and 81.3%, respectively (Fig. 1). Age, N-stage, HPV status and smoking status were all significantly associated with OS (Table 2).

## 4. Discussion

With regard to the ENI in HNSCC primarily treated with (chemo)radiation, the current standard of care is to electively irradiate both sides of the neck in order to reduce the risk of RF. The pivotal question is: to which extent ENI will prevent the occurrence of RF and specifically cRF? To the best of our knowledge, this is the first study primarily reporting on the incidence of cRF in electively treated contralateral neck in the IMRT-era. The current study showed 3-year cumulative incidences of 4.5% for RF in the electively irradiated volume, and 2.8% for cRF when bilateral ENI was given. About two-third of all patients with RF had ipsilateral recurrence and one-third of them had cRF. However, there were no statistically significant differences between patients with iRF and cRF with regard to the possibility to have salvage treatment or the rates of OS or CSS. Node-positive disease and HPV-negative oropharyngeal cancer were predictive factors for RF in general, and no specific risk factor was identified for cRF.

Although numerous studies reported on outcome of patients with HNSCC primarily treated with (chemo)radiation, studies on the incidence of RF in electively treated neck levels are scarce. In the seventies and eighties, different studies reported 1–8% incidence of RF in an electively treated neck [3,22–25]. However, the findings from these studies are barely applicable to the current clinical practice since these patient populations were treated with outdated 2-dimensional radiation techniques which are nowadays rarely used for the treatment of HNSCC, and these studies were published before the introduction of consensus guidelines for the delineation of the lymph node levels in HNSCC [20].

In the few IMRT-era studies that reported on the incidence of RF within an electively treated neck level, the incidence ranged between 1 and 11% [14–19]. Although Kjems et al. [14] focused in their study on the incidence of RF in retropharyngeal space and level IB, RF in electively treated neck levels was seen in 77 patients (11%). How many of the 77 cases of RF were cRF was not mentioned. They only mentioned that no cRF was seen in the retropharyngeal space and only 1 of 62 patients (1.6%) with oral cavity developed cRF. The incidence of RF in electively treated neck levels was 1% in the studies of Studer et al. [15] and Leeman et al. [16] In these studies the incidence of cRF was not reported. In the study of van den Bosch et al. [17], 14 out of 264 patients (5.3%) developed RF in electively treated neck. In their paper the incidence of RF in the contralateral neck was not reported. However, in personal communication, the authors of the paper indicate that in 6 patients (2.3%) the RF was seen in the electively treated contralateral neck. Gupta et al. [18] reported 2 cRF in their study population of 60 patients (3.3%). The findings of the last 2 studies correspond well with the cumulative incidence of cRF of 2.8% reported in the current study.

**Table 3**
Cox regression analysis of risk factors for death from any cause after regional failure.

| Death from any cause | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | p-value | HR | 95%CI | p-value |
| Laterality of RF (ref: ipsilateral) | 0.89 | 0.46–1.69 | 0.713 | | | |
| Salvage treatment of RF (ref: none) | 0.34 | 0.19–0.61 | **<0.001** | 0.37 | 0.19–0.72 | **0.003** |
| Age (ref: <65 years) | 1.70 | 0.98–2.98 | 0.061 | 1.33 | 0.72–2.47 | 0.367 |
| Smoking status (ref: non-smoker) | 2.00 | 0.90–4.44 | 0.088 | 1.19 | 0.49–2.89 | 0.697 |
| T-stage (ref: T1/T2) | 0.79 | 0.46–1.35 | 0.385 | | | |
| N-stage (ref: N0) | 1.83 | 0.82–4.07 | 0.141 | 1.95 | 0.83–4.60 | 0.128 |
| Tumorsite (ref: HPV-negative oropharynx) | | | | | | |
| HPV-positive oropharynx | 0.07 | 0.01–0.54 | **0.011** | 0.06 | 0.01–0.46 | **0.007** |
| Larynx | 0.79 | 0.40–1.54 | 0.492 | 0.74 | 0.37–1.49 | 0.397 |
| Hypopharynx | 1.07 | 0.52–2.20 | 0.864 | 0.99 | 0.45–2.15 | 0.971 |

Abbreviations: RF: regional failure; ref: reference category; HPV: human papilloma virus; PT: primary tumor; HR: hazard ratio; 95%CI: 95% confidence interval.

The question about the extent of the protection offered by bilateral ENI in terms of RF and cRF was raised by our group because we, as many other radiation oncologists, over time have come to believe that bilateral ENI is an overtreatment in the majority of patients with well-lateralized HNSCC. There is growing evidence that the incidence of cRF in well-selected HNSCC is very low, both in studies where unilateral ENI was applied [7,8], and in those where the neck dissection was proceeded by sentinel node procedure [26–29]. It is clear from the results of these studies that a less conservative approach with regard to the indication for unilateral ENI is justified. Therefore our group initiated the SUSPECT study, as a proof-of-concept (ClinicalTrials.gov Identifier NCT02572661) [30,31]. In this study, a SPECT/CT-guided approach was applied to select patients with lateralized T1-3N0-2b HNSCC for unilateral ENI. Patient without contralateral drainage were electively treated to one side of the neck. The accrual of this prospective study closed in October 2017, and the results of the study will be published soon.

This study is limited by its retrospective nature, though the chosen primary and secondary endpoints (cumulative incidences of RF, cRF and OS) seem robust. Its strengths are the large, consecutive patient cohort, the uniform staging and treatment regimen applied and the fact that data about the impact of bilateral ENI on the incidence of cRF is lacking. Although it was not surprising that the incidence of cRF in the current study was low after bilateral ENI (around 2.8%), we would like to put this finding in the perspective of the incidence of cRF after *unilateral* ENI being as low as 2.5% [7,8]. Therefore, we are making a plea for expanding the indication for unilateral ENI using smart image-guided tools to select patients at very low risk of cRF and offer these patients unilateral irradiation.

In conclusion, cRF still occurs in an estimated 2.8% of patients who were electively treated to contralateral neck and the cumulative incidence of RF after bilateral ENI was 4.5%. No specific risk factor was predictive for cRF. Notably, no differences were seen between iRF and cRF regarding the possibilities of salvage treatment or the rates of OS or CSS.

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## Conflicts of interest

The authors declare that they have no conflict of interest.

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