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▶ **To cite this version:**

Carole Pflumio, Idriss Troussier, Xu Shan Sun, Julia Salleron, Claire Petit, et al.. Unilateral or bilateral irradiation in cervical lymph node metastases of unknown primary? A retrospective cohort study. European Journal of Cancer, 2019, 111, pp.69 - 81. 10.1016/j.ejca.2019.01.004 . hal-03486172

HAL Id: hal-03486172
https://hal.science/hal-03486172

Submitted on 20 Dec 2021

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Version of Record: https://www.sciencedirect.com/science/article/pii/S0959804919300164
Manuscript_9ecde07726ca666145858505d280d2c1

Title: Unilateral or bilateral irradiation in cervical lymph node metastases of unknown primary? A retrospective cohort study

Short title: CUP and radiotherapy

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Financing: CHU de Besançon – CH de Belfort-Montbéliard - Institut de Cancérologie de Lorraine

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Abstract

Introduction: Patients with cervical lymphadenopathy of unknown primary carcinoma (CUP) usually undergo neck dissection and irradiation. There is an ongoing controversy regarding the extent of nodal and mucosal volumes to be irradiated. We assessed outcomes after bilateral or unilateral nodal irradiation. ***Methods:*** This retrospective multicentre study included patients with CUP and squamous cellular carcinoma who underwent radiotherapy between 2000 and 2015. ***Results:*** Of 350 patients, 74.5% had unilateral disease and 25.5% had bilateral disease. Of 297 patients with available data on disease and irradiation sides, sixty-one (20.5%) patients had unilateral disease and unilateral irradiation, 155 (52.2%) unilateral disease and bilateral irradiation and 81 (27.3%) bilateral disease and bilateral irradiation. Thirty-four (9.7%) and 217 (62.0%) patients received neoadjuvant and/or concomitant chemotherapy, respectively. Median follow-up was 37 months. Three-year local, regional, locoregional failure rates and CUP-specific survival were 5.6%, 11.7%, 15.0% and 84.7%, respectively. In patients with unilateral disease, the three-year cumulative incidence of regional/local relapse was 7.7%/4.3% after bilateral irradiation versus 16.9%/11.1% after unilateral irradiation (HR=0.56/0.61, p=0.17/0.32). The cumulative incidence of CUP-specific deaths was 9.2% after bilateral irradiation and 15.5% after unilateral irradiation (p=0.92). In multivariate analysis, mucosal irradiation was associated with better local control, while no neck dissection, ≥N2b and interruption of radiotherapy for more than four days were associated with poorer regional control. Toxicity was higher after bilateral irradiation (p<0.05). No PET-CT, largest node diameter, ≥N2b, neoadjuvant chemotherapy and interruption of radiotherapy were associated with poorer cause-specific survival. ***Conclusion:*** Bilateral nodal irradiation yielded non-significant better nodal and mucosal control rates but was associated with higher rates of severe toxicity.

Keywords: neoplasms, unknown primary - head and neck neoplasms, radiotherapy, neck dissection, chemotherapy

Introduction

Head and neck cancer of unknown primary (CUP) represents 1–4% of head and neck tumours [1, 2]. Their diagnostic work-up includes fine-needle aspiration of the node(s), PET-CT and panendoscopy usually with tonsillectomy and/or mucosectomy [3-11], as well as human papilloma virus (HPV) and Epstein Barr Virus (EBV) testing since the 2017 TNM classification [12]. Neck dissection is used both as a diagnostic and therapeutic modality. Irradiation aims to prevent regional relapse (≈10% of patients) [8, 13, 14] and metachronous mucosal failure of the upper aerodigestive tract (≈5–15%) [5, 9, 15]. A current area of controversy is whether selective or extensive irradiation of nodal areas should be performed, and whether de-escalation of mucosal irradiation can be performed based on the low relapse rates, toxicity of extensive irradiation and presumed rates of HPV-related carcinomas. On the other hand, intensity-modulated radiation therapy (IMRT) has improved the tolerance to extensive nodal and mucosal irradiation to the point where it may prevent more locoregional relapses than elective irradiation while minimizing toxicity [2, 16, 17]. Due to the rarity of CUP, however, the level of evidence is currently based only on retrospective studies of less than 200 patients [1, 18-24]**.** To date, no prospective randomized trial has ever been completed to advocate for or against either strategy, as the sole randomized trial (NCT00047125; unpublished) started was terminated early due to insufficient accrual.

We aimed to assess whether bilateral and unilateral nodal neck irradiation resulted in different outcomes in terms of local and regional control and of toxicities.

Material and methods

This institutional review board- and ethical committee-approved retrospective, multicentre and international study included patients irradiated for CUP between 2000 and 2015. Patients with squamous cell CUP were included after proper diagnostic work-up showing absence of distant metastases and a histology-proven diagnosis of carcinoma, and were treated with curative external beam radiotherapy. The diagnostic work up has changed over time. For example, the use of PET-CT has become more systematic after 2008 after demonstration of its performances in the detection of mucosal head and neck primaries [25]. Apart from PET-CT, the diagnostic work up of CUPs included FNA then panendoscopy and head neck and chest CT. Patients with adenocarcinomas (or non-squamous cell carcinomas), lymphomas, melanomas or sarcomas, or previous head and neck irradiation were excluded. Data were collected on https://www.easy-crf.com/ambicup/ (encrypted secured website) and included age, gender, imaging, nodal stage, extranodal spread, nodal diameter, histology, differentiation and HPV/EBV status. Treatment-related data included neck dissection, radiotherapy technique (three-dimensional (3D) or IMRT), total dose and fractions, interruption of radiotherapy, and target volumes: uni or bilateral nodal irradiation and their risk-dependent dose levels, pan-mucosal or elective or no mucosal irradiation, chemotherapy (neoadjuvant or concomitant).

We refer to microscopic mucosal disease turning into a macroscopic primary tumor if left untreated at the time of diagnosis of CUP. Of note, a second primary is usually defined as a primary tumor occurring in another site compared to first primary event. However, by definition CUP do not exhibit a primary. Another aspect of the definition for second primaries is time to occurrence later than 5 years after first event.

Patients underwent follow-up visits according to standards at their institutions and their physician's discretion. Acute and late toxicities were based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0 (from descriptions in charts).

Statistics

Quantitative parameters were described by median, mean and standard deviation, qualitative parameters by frequency and percentage. Missing data were not computed in the percentages. Regional failure was defined as the persistence or recurrence of tumoral lymph node(s) and local failure as emergence of primary in the mucosae of the upper aerodigestive tract. Local, regional and locoregional relapses were described with the Fine and Gray model, to take into account competing risks such as emergence of metastases or death whatever the cause. For CUP-specific survival, we only considered death due to head and neck cancer, and the Fine and Gray model was also computed to consider death due to other causes as a competing risk. The Kaplan–Meier method was performed to describe overall survival (OS) defined as the time lapse between the date of diagnosis and the date of death, whatever the cause. The prognostic value of each factor was studied using the bivariate Gray model, and the results were expressed with the hazard ratio (HR) and its 95% confidence intervals. The parameters with a p-value less than 0.1 in bivariate analysis were introduced in a multivariate Gray model, with backward selection. All statistical analyses were performed using SAS software (SAS Institute Inc., Cary, NC 25513). P-values <0.05 were considered statistically significant.

Results

From 2000 to 2015, 377 patients were irradiated for CUP, of whom 27 were excluded due to other histology (n=2), no radiotherapy (n=1) or insufficient follow-up data (n=20). Patient and tumour characteristics of the 350 patients treated in 20 institutions are presented in Table 1. Patients with N2a/b disease represented the majority of the population, but N3 disease was also frequently observed. A majority (74.5%) of patients had unilateral nodal disease, while 82 (25.5%) patients had N2c or bilateral N3 disease. Fifty-eight (70.7%) patients with bilateral disease had N3 presentation. Conventional squamous cell carcinomas accounted for 97.7% of all carcinomas. Human papilloma status was tested in only 58 patients and was positive in 18 of them. Before 2005, 15% of patients had a PET (or PET CT), in 2005 50% and after 2006, 95%.

Treatment characteristics are presented in Table 2. A majority of patients underwent neck dissection (74.4%), while the other patients were either inoperable or had unresectable disease. All had nodal irradiation and 304 (87.6%) had mucosal (elective or extended) irradiation. A majority of patients underwent concomitant chemotherapy (64.8%) and 9.8% had neoadjuvant chemotherapy. Among 297 patients with available data on disease and irradiation side, sixty-one (20.5%) patients had unilateral disease and underwent unilateral irradiation, 155 (52.2%) had unilateral disease and underwent bilateral irradiation and eighty-one (27.3%) patients had bilateral disease and bilateral irradiation. In 306 patients for whom target volume side was reported, there was 1% unilateral irradiation until 2008 (1/89). In contrast, after 2009, 29% of the patients underwent bilateral irradiation (63/216), $p<0.001$. Equal proportions of patients received 3D irradiation or IMRT. The oropharynx was the most commonly irradiated primary site (84.9%), while the nasopharynx, larynx and hypopharynx were irradiated in two-thirds of the patients and the oral cavity in less than a quarter of patients. Those N1 patients who underwent RT were included, there were 39 (11.5%) patients

with N1 disease presented in Table 1. One patient underwent radiochemotherapy exclusively, others underwent neck dissection then radiochemotherapy.

The median follow-up was 37 months (IQR: 24; 63). Out of 256 patients living at last follow-up, 64 (25.0%) patients had less than 24 months follow-up but at least three months follow-up. Crude failure rates are presented in Table 3. Ninety-three (26.6%) patients had an isolated or combined relapse at a median time of 12 months. Of these, there were 26 (7.4%) local relapses, 41 (11.7%) regional relapses and 46 (13.1%) metastatic relapses. Details of the patterns of failure are presented in Figure 1 (supplementary data). Among the five patients with bilateral nodal disease at diagnosis, four had bilateral relapse and one had unilateral relapse in the neck. Among the 36 patients with unilateral disease at diagnosis, 23 had unilateral relapse, seven had contralateral relapse and six patients had bilateral relapse. Of those patients with unilateral relapse, 19 had extended nodal irradiation (three patients without detailed nodal volume irradiation), with a median of five and a minimum of four nodal levels irradiated, suggesting that nodal relapse occurred in field. The median dose at the site of relapse was 54Gy (IQR 30; 60). Sixty-two (17.7%) patients died of head and neck cancer. At last follow-up, 64.3% (225) patients were alive without disease. Cumulative three-year incidence of local (Figure 2a), regional (Figure 2b) and locoregional (Figure 2c) failures were 5.6% [95%CI 3.1-8.1], 11.8% [95%CI 8.2-15.2] and 15.0% [95%CI 1.0-18.8], respectively. Three-year OS was 80.6% [95%CI 75.5-84.8] and cumulative incidence of CUP-specific death was 15.3% [95% CI 11.0-19.3]. Details of nodal and mucosal relapses are presented in supplementary data.

Prognostic factors of local, regional relapse and CUP-specific death are presented in Table 4. In multivariate analysis, mucosal irradiation was the only independent prognostic factor associated with better local control. There was no statistical difference between pan-mucosal and selective mucosal irradiation (HR 1.36 [0.48;3.86], p=0.55) among the 304 patients

undergoing mucosal irradiation. There was no significant association between irradiation of mucosal site (oral cavity, oropharynx, nasopharynx, larynx or hypopharynx) and mucosal relapse (Table 4). In multivariate analysis, advanced (N2b/c and N3) or early (N1 and N2a) disease, no neck dissection and interruption of radiotherapy for more than four days were prognostic factors of regional relapse.

In multivariate analysis, absence of PET-CT at diagnosis, largest nodal diameter, N2c/N3 disease, neoadjuvant chemotherapy and interruption of radiotherapy were prognostic factors of CUP-specific death. Metastatic relapse was less frequent in patients with a PET-CT at diagnosis or than in those without (data not shown). There were no toxic deaths, therefore toxicity does not explain the more frequent CUP-specific deaths associated with neoadjuvant chemotherapy (data not shown).

Unilateral or bilateral nodal irradiation resulted in statistically similar outcomes (Table 4) for 297 patients with available data on disease and irradiation side (Figure 4). However, in patients with unilateral disease, the cumulative three-year incidence of local relapse (Figure 3a) was 4.3% [95%CI 0.9-7.6] for those undergoing bilateral irradiation, while it was 11.1% [95%CI 2.3-19.2] in patients undergoing unilateral irradiation (p=0.32, HR 0.61 [95 CI 0.23-1.63]). Similarly, the cumulative incidence of regional failure (Figure 3b) was 7.7% [95%CI 3.2-11.9] for those undergoing bilateral irradiation, while it was 16.9% [95%CI 6.1-26.4] in patients undergoing unilateral irradiation (p=0.17, HR 0.56 [95 CI 0.25-1.27]). Locoregional incidence is shown in Figure 3c. Again, the cumulative incidence of CUP-specific deaths (Figure 3d) was 9.2% [95%CI 4.1-14.0] for those patients undergoing bilateral irradiation, while it was 15.5% [95%CI 4.1-25.6] in patients undergoing unilateral irradiation (p=0.92, HR 1.04[95% CI 0.45-2.41]). The third group of patients, i.e. those patients with bilateral

disease at diagnosis who underwent bilateral irradiation, had a cumulative incidence of CUP-specific deaths of 26.9% [95%CI 15.1-37.0] (p=0.06 HR=2.28[95% CI 0.95-5.44]).

There was no significant difference between <=2008 versus >2008 in terms of local relapse, regional relapse or CUP-related death (data not shown).

Acute and late toxicities

Severe (grade 3–4) acute and late toxicities are presented in Table 5. They were assessed in 301 (86.0%) patients. There were no grade 5 (lethal) toxicities. Acute toxicities mostly consisted of dysphagia, mucositis and pain. Severe dysphagia and pain were more frequent in cases of bilateral nodal irradiation (both $p<0.01$). Late toxicities, which occurred in less than 15% of all patients, mainly consisted of severe xerostomia, dysphagia and fibrosis. Severe xerostomia and dysphagia were more frequent after bilateral nodal irradiation (both $p<0.01$). Toxicities were responsible for treatment interruption of four consecutive days or more in 23 (6.6%) patients.

Bilateral irradiation was performed with 3D in 52% of patients (127/242), while unilateral irradiation was performed with 3D in 16% of cases (10/64, $p<0.001$) only. There was a trend for more toxicities with bilateral 3D irradiation vs IMRT in case in bilateral disease. Patients undergoing bilateral irradiation (n=242) with 3D irradiation vs IMRT had similar rates of severe acute toxicities but more late fibrosis (12.1% (15) vs 0.9% (1); $p<0.01$), xerostomia (25.8% (32) vs 6.3% (7); $p<0.01$) and dysphagia (15.3% (19) vs 2.7% (3); $p<0.01$).

Discussion

With 350 patients, the present study is the largest to date in a rare subgroup of head and neck cancers, and it specifically addressed "standard" bilateral extended nodal volume irradiation versus de-escalation with unilateral (often elective) nodal irradiation in patients with CUP. Most patients underwent bilateral irradiation; 52.2% of them had bilateral irradiation for unilateral nodal disease, while 20.5% of them had unilateral irradiation for unilateral disease. Of note, IMRT became a standard of care in head and neck cancers in 2011 [2]. While some institutions have been advocating unilateral irradiation since around 1995 because of concerns around rare locoregional events and radiation toxicities, others have moved toward IMRT-based bilateral irradiation to decrease the rate of toxicities while maintaining excellent locoregional control rates. As a result, half the patients of this series were treated with IMRT. Our results suggest that some late toxicities after bilateral 3D irradiation can be avoided with IMRT. Thus, toxicities following bilateral or unilateral irradiation should be investigated in larger IMRT studies.

The present study shows that the regional control rate and occurrence of mucosal primaries did not differ between patients who had unilateral irradiation and those who had bilateral irradiation. However, as observed on curves of cumulative events in patients with unilateral disease at diagnosis, patients with bilateral irradiation appeared to do better compared to patients undergoing unilateral irradiation. Consistent with other series**,** the number of events was low, as 11.7% of patients had a regional relapse, and 7.4% had a mucosal failure during follow-up but the median follow-up was limited to 37 months (IQR: 24; 63). For Ligey *et al*, the nodal relapse rate was 34% after unilateral neck irradiation and 25% after bilateral radiotherapy ($p = 0.21$) after a median follow-up of 3.3 years. A primary head and neck tumour occurred in 12% after unilateral irradiation and 6% after bilateral radiotherapy (difference not significant) [22-24]**.** The original hypothesis was that unilateral irradiation

would be responsible for 15% more relapses than bilateral irradiation. However, a quarter of patients had bilateral disease at diagnosis and half the patients underwent 3D irradiation. Thus, we will investigate whether the benefit of bilateral irradiation in patients with unilateral disease might become significant (with a power of 80%) in a larger study which includes 591 additional patients, with 272 patients undergoing unilateral IMRT. We will also assess the ongoing trend to de-escalate nodal and mucosal radiotherapy volume, and ultimate disease control after salvage treatment of nodal and/or mucosal failures. On the other hand, this present study shows that both selective and pan-mucosal irradiation, the latter extending from the nasopharynx to the hypopharynx and larynx, helped to avoid mucosal failures and allowed a significant CUP-specific survival benefit compared to no mucosal irradiation. Further data are needed to investigate whether elective mucosal irradiation yields similar local control to, and fewer late severe toxicities than, pan-mucosal irradiation. Altogether, our observations favour bilateral nodal irradiation and mucosal irradiation.

As for nodal control, advanced stage and no neck dissection were associated with poorer regional control. As most patients were French, they underwent upfront neck dissection per national CUP policy. Thus, patients undergoing non-surgical options upfront and no neck dissection afterwards [26] were an unfavourable group, and neoadjuvant chemotherapy did not compensate for their poorer prognosis. Moreover, neck dissection improves locoregional control but not survival in the era of chemoradiation for CUP. For example, in a meta-analysis by Balaker *et al*, patients who underwent neck dissection with either postoperative radiation or chemoradiation had a 5-year survival of 52.4% compared to 46.6% for those treated with chemoradiation alone; however, this difference was not statistically significant [27-29]. Omission of neck dissection, which is responsible for shoulder, neural (XI) and swallowing morbidity, was not our study aim and was not evaluated in our series due to neck dissection policy.

Interestingly, in addition to advanced nodal stage and size [28, 29], neoadjuvant chemotherapy and interruption of radiotherapy, the fact that absence of PET-CT at diagnosis had a negative effect on CUP-specific survival is intriguing. It is possible that patients not undergoing PET-CT at diagnosis were more likely to have subclinical metastases, and so died of symptomatic metastases later in follow-up, than those with no metastases on PET-CT [25]. Another hypothesis is that PET-CT improves the definition of nodal target volumes before neck dissection and irradiation [30]. In contrast to neoadjuvant chemotherapy, concomitant chemotherapy was not associated with poorer prognosis. Most patients received cisplatin where poor prognostic factors, as defined in other head and neck cancers [31, 32], were identified following evaluation of the neck dissection specimen.

Study limitations include the lack of systematic HPV testing. However, to date, HPV testing is only recommended in oropharyngeal cancers and EBV for nasopharyngeal cancers only. Reporting of HPV or EBV status has not been standard practice in participating institutions. In this series, all patients had unknown primaries (T0) after thorough diagnostic locoregional and distant procedures. While recent retrospective studies suggest that HPV testing should be systematic [34] to advocate treatment de-escalation [33, 35, 36], such data may be premature if the unknown (yet microscopic) primary indeed resides in the larynx or hypopharynx. In our series, only five out the 26 mucosal relapses occurred in the oropharynx only. Whether HPV-guided de-escalation of radiotherapy volumes is relevant regardless of the involved neck level(s) is questionable given the results of our study. Such a strategy might better apply to cystic nodes and/or levels 2 and 3, and should be investigated with more stringent methodology. The TNM 2017 classification might be overemphasizing the value of HPV testing. As suggested by the landmark Lindberg study in 1972, the risk for nodal involvement can be estimated based on the primary location. The reverse may be applied for CUPs.

There could be an effect of time and that was indeed our initial hypothesis but there was however no significant difference between <=2008 versus >2008 in terms of local relapse, regional relapse or CUP-related death in our study. We had observed a progressive switch in practice despite 1/ no or very limited level of evidence in favour of unilateral irradiation rather than bilateral irradiation 2/ no major event in favour of unilateral irradiation 3/ the possibility to limit the morbidity of irradiation (and in particular bilateral irradiation) with IMRT. To investigate the latter hypothesis, the length of the study rather appears as a strength as we could collect data from patients with similar disease presentation but undergoing either 3D or IMRT.

Trends in PET CT have clearly changed dramatically over years. We analyzed rates more specifically. Before 2005, 15% of patients had a PET (or PET CT), in 2005 50% and after 2006, 95%. There was however no impact of PET CT on locoregional control. It was related to CUP-specific death. Our hypothesis is that metastatic patients were excluded while some may have been included in the study if they had had no PET CT due to undiagnosed metastases.

Missing data are clearly a weakness as in many retrospective studies, but it is indicated and even with incomplete patient data for certain items, this remains a large study compared to other CUP publications (297 patients with available data on disease and irradiation sides out of 350 patients=84%). Of note, the 53 patients with missing data on disease and irradiation sides had comparable characteristics than the others (data not show). Consequently, the 297 patients are representative for the whole population. Unfortunately, the location of the initial nodal desease is missing but N-stage and unilateral/bilateral desease are clearly specified. By being multicentric, we may consider that this study allowed for investigating the impact of dose and technique, in contrast to a monocentric with single practice.

16 000 new head and neck cases are diagnosed in France; ie about 600 cases with CUPs. It is difficult to get exhaustivity in retrospective studies but we tried to have a representation of differents kinds of health care institutions (private, public, tertiary versus regional centers etc). Thus the number achieved is representative and relevant to investigate radiation practice thus it is a full overview.

Conclusion

This large study of cervical lymphadenopathies of unknown primary suggests that unilateral neck irradiation may not yet be the treatment standard, as it may result in slightly worse rates of mucosal and nodal relapse. Severe toxicities were, however, more frequent after bilateral irradiation than unilateral irradiation. Molecular biomarkers are probably necessary to better predict the primary site of origin in a way that is adapted for the neck levels involved. However, not all CUPs are HPV-positive. Thus, de-escalation of the volumes of nodal and/or mucosal irradiation with IMRT should be investigated further. The prognostic impact of the 8th TNM 2017 classification, which takes into account EBV and HPV in CUP, should also be assessed. We are continuing this study so as to collect enough patients to reach sufficient power.

Acknowledgements: The manuscript has been revised for the English by an independent scientific language editing service (Angloscribe).

Conflict of interest statement: The authors have declared no conflicts of interest with respect to the study

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Tables and Figures

Figures: no color necessary

Figure 1 (supplementary data): patterns of failure

Figure 2 a, b, and c: Cumulative incidence of local relapses, regional relapses and cause-specific deaths for all patients

Figure 3 a, b, c and d: Cumulative incidence of local relapses, regional relapses, locoregional relapses and cause-specific deaths for the 297 patients with available data on disease and irradiation side

Figure 4: Distribution of the site of treatment failure

Tables

Table 1: Patient and tumour characteristics

Footnotes: Results presented with frequency and percentage (n%) or by median; mean ± standard deviation. CT, Computerized tomography; HPV, Human papillomavirus; MRI, Magnetic resonance imaging; NOS, Not otherwise specified; SCC, Squamous cell carcinoma; 18FDG PET, 18Fluorodeoxyglucose positron emission tomography

*Missing data >10%: Differentiation = 53, Extranodal spread = 37, HPV = 292

Table 2: Characteristics of irradiation, surgery and other antineoplastic treatments

Footnotes: Results presented with frequency and percentage (n%) or by median; mean ± standard deviation

IMRT, Intensity-modulated radiation therapy; Gy, Gray; Uni-D Uni-I, unilateral disease at diagnosis undergoing unilateral irradiation; Uni-D Bi-I, unilateral disease at diagnosis

undergoing bilateral irradiation; Bi-D Bi-I, Bilateral disease at diagnosis undergoing bilateral irradiation; NRT, Nodal radiotherapy; HR, High risk level; IR, Intermediate risk level; LR, Low risk level

*Missing data >10%: Group = 53, RTN dose level = 42, Radiotherapy target volume = 44

Table 3: Description of crude rates of each outcome over all follow-up period and status on last follow-up.

Footnotes: Results presented with frequency and percentage (n%) or by median; mean ± standard deviation. Gy, Gray; RP, retropharyngeal lymph nodes

Table 4: Prognostic factors of local and regional relapse and cause-specific death in bivariate and multivariate analyses using the Gray model for competing risk data

Footnotes: *Variables included in multivariate analysis with backward selection. HR 95% CI, Hazard ratio 95% confidence interval; 18 FDG PET, 18Fluorodeoxyglucose positron emission tomography; SCC, Squamous cell carcinoma; IMRT, Intensity-modulated radiation therapy; 3D, Three-dimensional; Uni-D Uni-I, unilateral disease at diagnosis undergoing unilateral irradiation; Uni-D Bi-I, unilateral disease at diagnosis undergoing bilateral irradiation; Bi-D Bi-I, Bilateral disease at diagnosis undergoing bilateral irradiation; Gy, Gray; RTN, Nodal radiotherapy; HR, High risk level; IR, Intermediate risk level; LR, Low risk level; RT, radiotherapy

Table 5: Acute and late adverse events grade 3–4. Footnotes: Nc, Not calculated; RTN, Nodal radiotherapy. Results expressed with frequency and percentages

Table 6 (supplementary data): Sides of mucosal and regional relapses

Table 1: Patient and tumour characteristics

Characteristics	
Age (years)	61.6; 62.4±10.2
Male gender	290 (82.9%)
Initial imaging	
Aerodigestiv tract endoscopy under general anaesthesia	329 (96%)
Head and neck CT	330 (94.6%)
Head and neck MRI	48 (13.8%)
Chest abdomen pelvis CT	190 (56.7%)
18FDG PET-CT	285 (82.1%)
Histology	
Conventional squamous cell carcinoma (SCC)	342 (97.7%)
SCC variant	8 (2.3%)
Differentiation*	
Well differentiated	125 (42.1%)
Keratinizing	90 (30.3%)
Non-keratinizing	24 (8.1%)
Not otherwise specified (NOS)	11 (3.7%)
Moderately differentiated	79 (26.6%)
Poorly differentiated	82 (27.6%)
Undifferentiated	11 (3.7%)
HPV positive* (58 tested)	18 (31.0%)
Nodal stage	
N1	39 (11.5%)
N2a	70 (20.6%)
N2b	117 (34.5%)
N2c	24 (7.1%)
N3	89 (26.3%)
Unilateral nodal disease	240 (74.5%)
Bilateral nodal disease	82 (25.5%)
Extranodal spread*	222 (70.9%)
Diameter of largest node (cm)	4.5; 5.6±6.0

Results presented with frequency and percentage (n%) or by median; mean ± standard deviation

CT, Computerized tomography; HPV, Human papillomavirus; MRI Magnetic resonance imaging; NOS, Not otherwise specified; SCC, Squamous cell carcinoma; 18FDG PET, 18Fluorodeoxyglucose positron emission tomography

*Missing data >10%: Differentiation = 53, Extranodal spread = 37, HPV = 292. Totals account for missing data, percentages are calculated with known data only

Table 2: Characteristics of irradiation, surgery and other antineoplastic treatments

Characteristics	
Surgery	
Tonsillectomy	101 (29%)
Neck dissection	259 (74.4%)
Radiotherapy	350 (100%)
IMRT	177 (50.6%)
Duration of radiotherapy (days)	49.0; 48.6±10.9
Nodal irradiation	350 (100%)
Total dose (Gy)	66.0; 64.0±6.9
≤ 56	47 (13.4%)
> 56 and ≤ 63	34 (9.7%)
> 63	269 (76.9%)
Number of fractions	33.0; 32.0±4.7
Group (n=297*)	
Unilateral disease & unilateral irradiation	61 (20.5%)
Unilateral disease & bilateral irradiation	155 (52.2%)
Bilateral disease & bilateral irradiation	81 (27.3%)
Radiotherapy target volume (n=306*)	
High-risk nodal level	254 (81.9%)
Dose (Gy)	66.0; 65.8±5.1
Ipsilateral / Bilateral / None	226 (73.9%) / 28 (9.2%) / 52 (17.0%)
Intermediate risk nodal level	136 (43.7%)
Dose (Gy)	59.4; 58.8±4.5
Ipsilateral / Contralateral / Bilateral / None	93 (30.4%) / 5 (1.6%) / 37 (12.1%) / 171 (55.9%)
Low risk nodal level	275 (89.0%)
Dose (Gy)	50.0; 51.8±3.0
Ipsilateral / Contralateral / Bilateral / None	50 (16.3%) / 39 (12.8%) / 186 (60.8%) / 31 (10.1%)
Mucosal irradiation	304 (87.6%)
Total dose (Gy)	50.0; 53.6±5.9
Number of fractions	25.0; 28.1±4.6
Target volume	
Nasopharynx including unilateral / bilateral irradiation	221 (66.4%) / 39 (17.9%) / 179 (82.1%)
Oropharynx including unilateral / bilateral irradiation	292 (84.9%) / 59 (20.6%) / 227 (79.4%)
Hypopharynx including unilateral / bilateral irradiation	258 (75.4%) / 39 (15.5%) / 213 (84.5%)
Larynx including unilateral / bilateral irradiation	219 (64.4%) / 20 (9.4%) / 194 (90.7%)
Oral cavity including unilateral / bilateral irradiation	77 (23.8%) / 24 (32.4%) / 50 (67.6%)
Chemotherapy	226 (64.8%)
Neoadjuvant	34 (9.8%)
Concomitant	217 (62.2%)

Results presented with frequency and percentage (n%) or by median; mean ± standard deviation
IMRT, Intensity-modulated radiation therapy; Gy, Gray; Uni-D Uni-I, unilateral disease at diagnosis undergoing unilateral irradiation; NRT, Nodal radiotherapy

*Missing data >10%: Group = 53, RTN dose level = 42, Radiotherapy target volume = 44. Totals account for missing data, percentages are calculated with known data only

Table 3: Description of crude rates of each outcome

Any relapse	93 (26.6%)
Mean delay of relapse (months)	11.7; 20.3±22.6
Local (mucosal) relapse of the head and neck	26 (7.4%)*
Several sites	5
Hypopharynx	6
Oropharynx	5
Oral cavity	5
Nasopharynx	1
Larynx	0
Unspecified	4
Regional relapse (nodes)	41 (11.7%)
Contralateral relapse	7
Ipsilateral relapse (including 1 with bilateral disease)	24
Bilateral relapse (4 bilateral disease and 6 unilateral disease)	10
Metastatic relapse*	46 (13.1%)
Lung	27
Bone	15
Liver	6
Mediastinum	7
Brain	3
Skin	3
Other	4
Second cancer (non-head and neck)	5
Status on last follow-up	
Dead due to head and neck cancer	62 (17.7%)
Dead due to other cancer	17 (4.9%)
Dead due to other cause (not cancer)	15 (4.3%)
Alive with active disease	31 (8.9%)
Alive without disease	225 (64.2%)

Legend: Gy, Gray; RP, retropharyngeal lymph nodes
Results presented with frequency and percentage (n%) or by median; mean ± standard deviation
*Totals are not necessarily equal to the sum of events because there may be several synchronous events
Totals account for missing data, percentages are calculated with known data only

Table 4: Prognostic factors of local and regional relapse and cause-specific death in bivariate and multivariate analyses using the Gray model for competing risk data

	Local relapse				**Regional relapse**				**CUP Specific death**			
	Bivariate analyses		Multivariate analysis		Bivariate analyses		Multivariate analysis		Bivariate analyses		Multivariate analysis	
	HR 95% CI	p	HR 95% CI	p	HR 95% CI	p	HR 95% CI	p	HR 95% CI	p	HR 95% CI	p
Patients and tumours												
Male gender	2.55 [0.62 ;10.60]	0.20			1.52 [0.60 ;3.85]	0.37			3.15 [1.15 ;8.67]	0.03*		
Age	1.04 [1.0 ;1.09]	0.07*			1.02 [1.00 ;1.05]	0.11			1.00 [0.97 ;1.02]	0.84		
18FDG PET	0.63 [0.28 ;1.43]	0.27			0.84 [0.40 ;1.79]	0.66			0.41 [0.24 ;0.71]	<0.01*	0.43 [0.23 ;0.80]	<0.01
Neck dissection	0.87 [0.36 ;2.08]	0.76			0.39 [0.21 ;0.73]	<0.01*	0.43 [0.23 ;0.83]	0.01	0.70 [0.40 ;1.23]	0.22		
Diameter of largest node (cm)	0.99 [0.95 ;1.03]	0.65			1.02 [0.99 ;1.06]	0.17			1.06 [1.04 ;1.08]	<0.01*	1.06 [1.03 ;1.09]	<0.01
TNM												
N1+N2a	1				1		1		1		1	
N2b	0.69 [0.24 ;2.00]	0.50			2.13 [0.82 ;5.53]	0.12	2.34 [0.92 ;5.96]	0.07	1.54 [0.74 ;3.19]	0.25	1.07 [0.46 ;2.47]	0.87
N2c+N3	1.24 [0.49 ;3.13]	0.65			3.94 [1.61 ;9.66]	<0.01*	3.49 [1.43 ;8.49]	<0.01	3.67 [1.87 ;7.21]	<0.01*	2.68 [1.32 ;5.43]	<0.01
Extranodal spread	1.03 [0.41 ;2.59]	0.95			1.69 [0.74 ;3.87]	0.21			2.24 [1.06 ;4.73]	0.04*		
SCC	0.64 [0.16 ;2.68]	0.55			0.71 [0.23 ;2.23]	0.56			0.82 [0.30 ;2.25]	0.70		
Differentiation												
Well differentiated	1				1				1			
Moderate+poor+undifferentiated	1.76 [0.65 ;4.75]	0.27			0.53 [0.28 ;0.99]	0.047*			0.70 [0.41 ;1.20]	0.20		
Nodal irradiation												
Radiotherapy technique												
3D	1				1				1			
IMRT	1.91 [0.88 ;4.12]	0.10			1.18 [0.63 ;2.19]	0.61			0.64 [0.37 ;1.12]	0.12		
Group												
Unilateral disease & unilateral irradiation	1				1				1			
Unilateral disease & bilateral irradiation	0.61 [0.23 ;1.63]	0.32			0.56 [0.25 ;1.27]	0.166			1.04 [0.45 ;2.41]	0.92		
Bilateral disease & bilateral irradiation	0.58 [0.19 ;1.80]	0.35			1.16 [0.50 ;2.67]	0.74			2.28 [0.95 ;5.44]	0.06*		
Total dose (Gy)												
≤ 56	1				1				1			
> 56 and ≤ 63	1.96 [0.33 ;11.82]	0.46			0.68 [0.12 ;3.86]	0.66			2.30 [0.74 ;7.17]	0.15		
> 63	1.73 [0.40 ;7.58]	0.46			1.49 [0.52 ;4.30]	0.46			1.74 [0.68 ;4.48]	0.25		
Nodal high-risk level irradiation	1.52 [0.46 ;5.05]	0.49			2.57 [0.77 ;8.57]	0.13			4.23 [1.29 ;13.84]	0.02*		
Nodal medium-risk level irradiation	1.31 [0.59 ;2.91]	0.51			0.67 [0.34 ;1.32]	0.25			1.58 [0.92 ;2.71]	0.10*		
Nodal low-risk level irradiation	0.82 [0.24 ;2.84]	0.76			1.47 [0.45 ;4.80]	0.52			0.97 [0.42 ;2.28]	0.95		
RT interruption ≥ 4 days	2.45 [0.81 ;7.42]	0.11			3.48 [1.47 ;8.21]	0.0045*	3.39 [1.46 ;7.88]	<0.01	3.23 [1.57 ;6.63]	<0.01*	3.81 [1.71 ;8.50]	<0.01
Mucosal irradiation												
Mucosal irradiation	0.30 [0.13 ;0.69]	<0.01*	0.30 [0.13 ;0.69]	<0.01	0.70 [0.31 ;1.57]	0.39			0.64 [0.33 ;1.26]	0.20		
Total dose > 50 Gy	2.10 [0.84 ;5.28]	0.11										
Nasopharynx	0.56 [0.21 ;1.50]	0.25										
Oropharynx	0.33 [0.04 ;2.74]	0.31										
Hypopharynx	1.09 [0.25 ;4.74]	0.91										
Larynx	2.19 [0.51 ;9.48]	0.30										
Oral cavity	2.31 [0.90 ;5.96]	0.08										
Chemotherapy												
Neoadjuvant	1.14 [0.34 ;3.86]	0.83			2.78 [1.33 ;5.80]	<0.01*			2.53 [1.27 ;5.06]	<0.01*	2.52 [1.19 ;5.33]	0.02
Concomitant	0.48 [0.22 ;1.03]	0.06*			0.98 [0.52 ;1.83]	0.94			0.85 [0.52 ;1.39]	0.51		

*Variables included in multivariate analysis with backward selection

HR 95% CI, Hazard ratio 95% confidence interval; 18 FDG PET, 18Fluorodeoxyglucose positron emission tomography; SCC, Squamous cell carcinoma; IMRT, Intensity-modulated radiation therapy; 3D, Three-dimensional; Uni-D Uni-I, unilateral disease at diagnosis undergoing unilateral irradiation; Uni-D Bi-I, unilateral disease at diagnosis undergoing bilateral irradiation; Bi-D Bi-I, Bilateral disease at diagnosis undergoing bilateral irradiation; Gy, Gray; NRT, Nodal radiotherapy; HR, High risk level; IR, Intermediate risk level; LR, Low risk level; RT, radiotherapy

Table 5: Acute and late adverse events grade 3–4 for the 297 patients with an available evaluation according to the side of irradiation and technique.

	Global	Unilateral NRT	Bilateral NRT	p	Unilateral NRT			Bilateral NRT		
					2D or 3D	**IMRT**	p	**2D or 3D**	**IMRT**	p
Number of available data	297	64	242		10	54		127	115	
Acute toxicities										
Dysphagia	78 (26.2%)	8 (12.7%)	70 (29.8%)	<0.01	0% (0)	15.1% (8)	0.33	33.1% (41)	26.1% (29)	0.25
Mucositis	69 (23.3%)	10 (16.4%)	59 (25.1%)	0.15	11.1% (1)	17.3% (9)	1	29.0% (36)	20.7% (23)	0.14
Pain	45 (15.0%)	4 (6.3%)	41 (17.3%)	0.03	0% (0)	7.4% (4)	Nc	15.9% (20)	18.9% (21)	0.54
Dermatitis	0 (0%)	0 (0%)	0 (0%)	Nc	0	0		0	0	
Other acute toxicity	11 (3.6%)	2 (3.2%)	9 (3.8%)	1	10% (1)	1.96% (1)		6(4.8%)	3(2.7%)	0.51
Late toxicities										
Xerostomia	40 (13.5%)	1 (1.6%)	39 (16.5%)	<0.01	10% (1)	0% (0)	Nc	25.8% (32)	6.3% (7)	<0.01
Dysphagia	22 (7.4%)	0 (0%)	22 (9.3%)	<0.01	0	0		15.3% (19)	2.7% (3)	<0.01
Fibrosis	18 (6.1%)	2 (3.3%)	16 (6.8%)	0.54	10% (1)	1.96% (1)	Nc	12.1% (15)	0.9% (1)	<0.01
Pain	8 (2.7%)	1 (1.6%)	7 (3.0%)	1	0% (0)	1.96% (1)	Nc	4.84% (6)	0.9% (1)	0.13
Osteonecrosis	4 (1.3%)	0 (0%)	4 (1.7%)	Nc	0	0		3.23% (4)	0% (0)	0.12
Second cancer	4 (1.3%)	0 (0%)	4 (1.7%)	Nc	0	0		3.2%(4)	0	0.12
Oesophageal stricture	3 (1.0%)	0 (0%)	3 (1.3%)	Nc	0	0		2.42% (3)	0% (0)	0.26
Trismus	1 (0.3%)	0 (0%)	1 (0.4%)	Nc	0	0		0.81% (1)	0% (0)	Nc
Other	8 (2.7%)	1 (1.6%)	7 (3.0%)	1	1(10.0%)	0	Nc	4.0% (5)	1.8%(2)	0.45

Nc, Not calculated; NRT, Nodal radiotherapy. Results expressed with frequency and percentages
Totals account for missing data, percentages are calculated with known data only

Side of regional relapse for bilateral disease according to radiotherapy target volume

Side of relapse for bilateral disease	Radiotherapy target volume		
	High-risk nodal level	Intermediate risk nodal level	Low risk nodal level
Bilateral	X		X
Bilateral	X	X	X
Bilateral			X
Bilateral	X		X
Unilateral	X		X

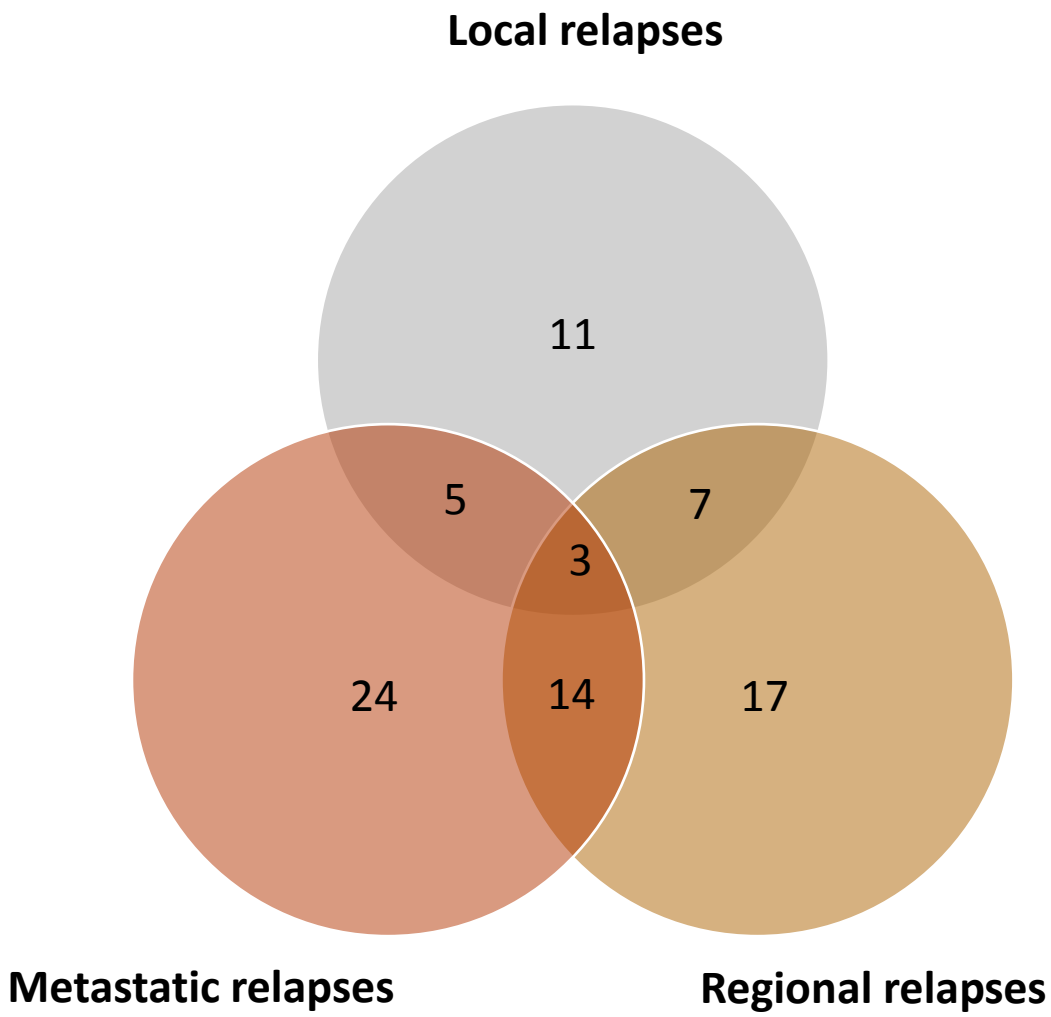
Side of regional relapse for unilateral disease according to radiotherapy target volume for ipsilateral and contralateral sides

Side of relapse for unilateral disease	Radiotherapy target volume					
	Ipsilateral			Contralateral		
	High-risk nodal level	Intermediate risk nodal level	Low risk nodal level	High-risk nodal level	Intermediate risk nodal level	Low risk nodal level
Bilateral	X	X				
Bilateral	X	X	X			X
Bilateral	X		X			X
Bilateral	X	X		X	X	
Bilateral	X	X	X			X
Bilateral	X		X			
Contralateral	X		X			X
Contralateral	X					
Contralateral	X		X	X		X
Contralateral	X		X			
Contralateral	missing	missing	missing	missing	missing	missing
Contralateral	X		X			X
Contralateral	X		X			
Ipsilateral	X		X			X
Ipsilateral	X		X			X
Ipsilateral	X	X				X
Ipsilateral	X		X			X
Ipsilateral	X	X	X		X	X
Ipsilateral		X				X
Ipsilateral	X	X				X
Ipsilateral	X		X			
Ipsilateral	X					X
Ipsilateral	X		X			X
Ipsilateral	X					X
Ipsilateral	X		X			
Ipsilateral	X	X				X
Ipsilateral	X	X	X			X
Ipsilateral	X		X			X
Ipsilateral	missing	missing	missing	missing	missing	missing
Ipsilateral	X					X
Ipsilateral	X		X			
Ipsilateral	missing	missing	missing	missing	missing	missing
Ipsilateral	missing	missing	missing	missing	missing	missing
Ipsilateral	X	X	X		X	X
Ipsilateral	X		X			X
Ipsilateral	X	X	X			

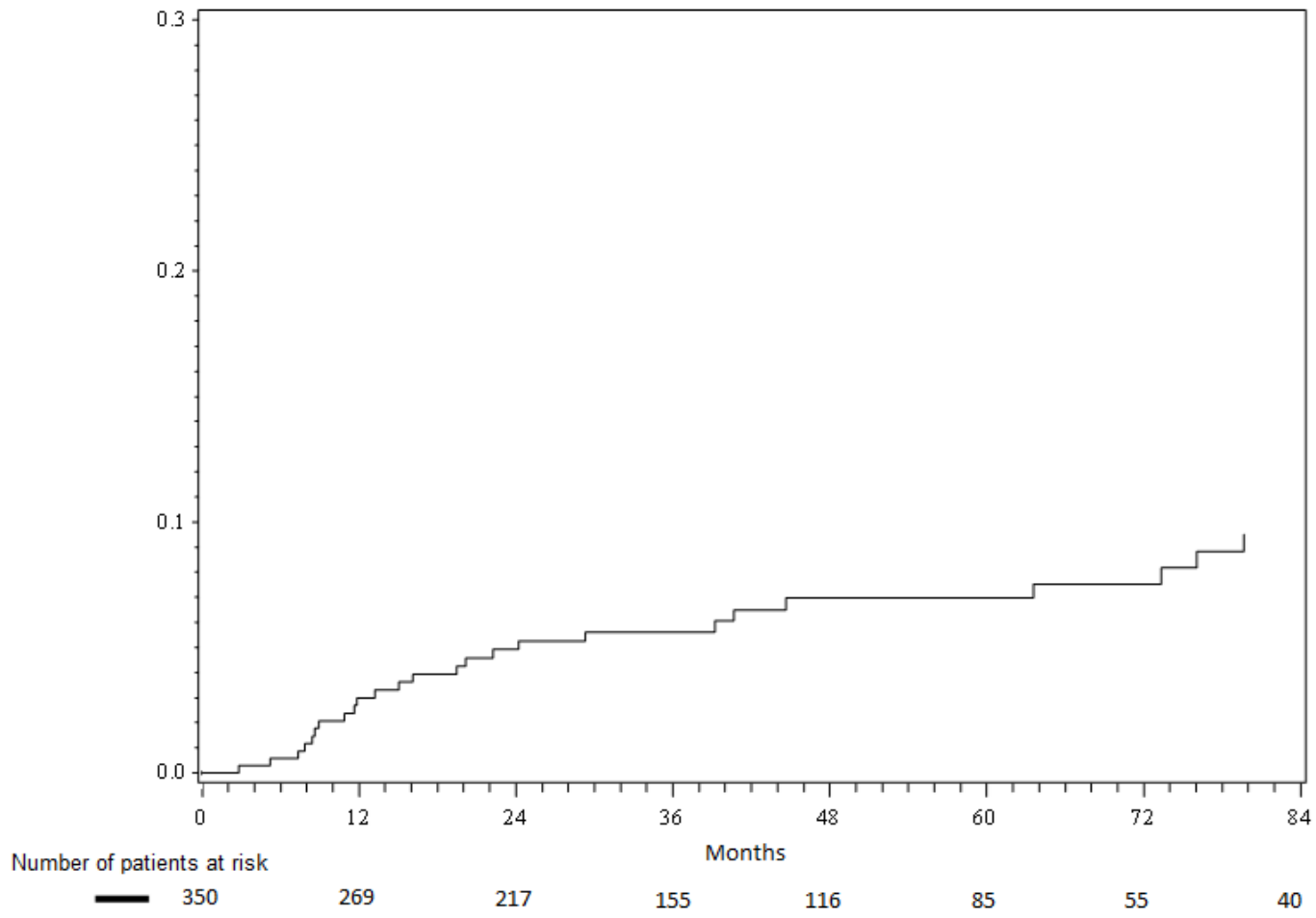
Details of mucosal local relapse

Details of primary relapse												In field relapse
nasopharynx		oropharynx		oral cavity		larynx		hypopharynx		others		
relapse	irradiation	relapse	irradiation	relapse	irradiation	relapse	irradiation	relapse	irradiation	relapse	irradiation	
unspecified												
	BI		BI				BI		BI	X		
	BI		BI				BI		BI	X		
			BI						BI		Yes[1]	
			BI		BI					X		
			UI		UI		UI		UI			
			BI				BI		BI	X		X
unspecified												X
											Yes[2]	X
	BI		BI	X			BI		BI			
	BI		BI	X	BI		BI		BI			
								X				
	BI		BI	X	BI		BI		BI			
	BI		BI	X			BI		BI			
								X				
	BI		BI		BI		BI	X	BI			X
		X	BI				BI	X	BI			X
	BI	X	BI				BI		BI			X
		X										X
X	BI		BI	X	UI		BI		BI			X
	UI		UI		UI		UI	X	UI			X
	BI		BI		BI		BI	X	BI	X		X
	BI	X	BI				UI		UI			X
		X										X
unspecified												
unspecified												

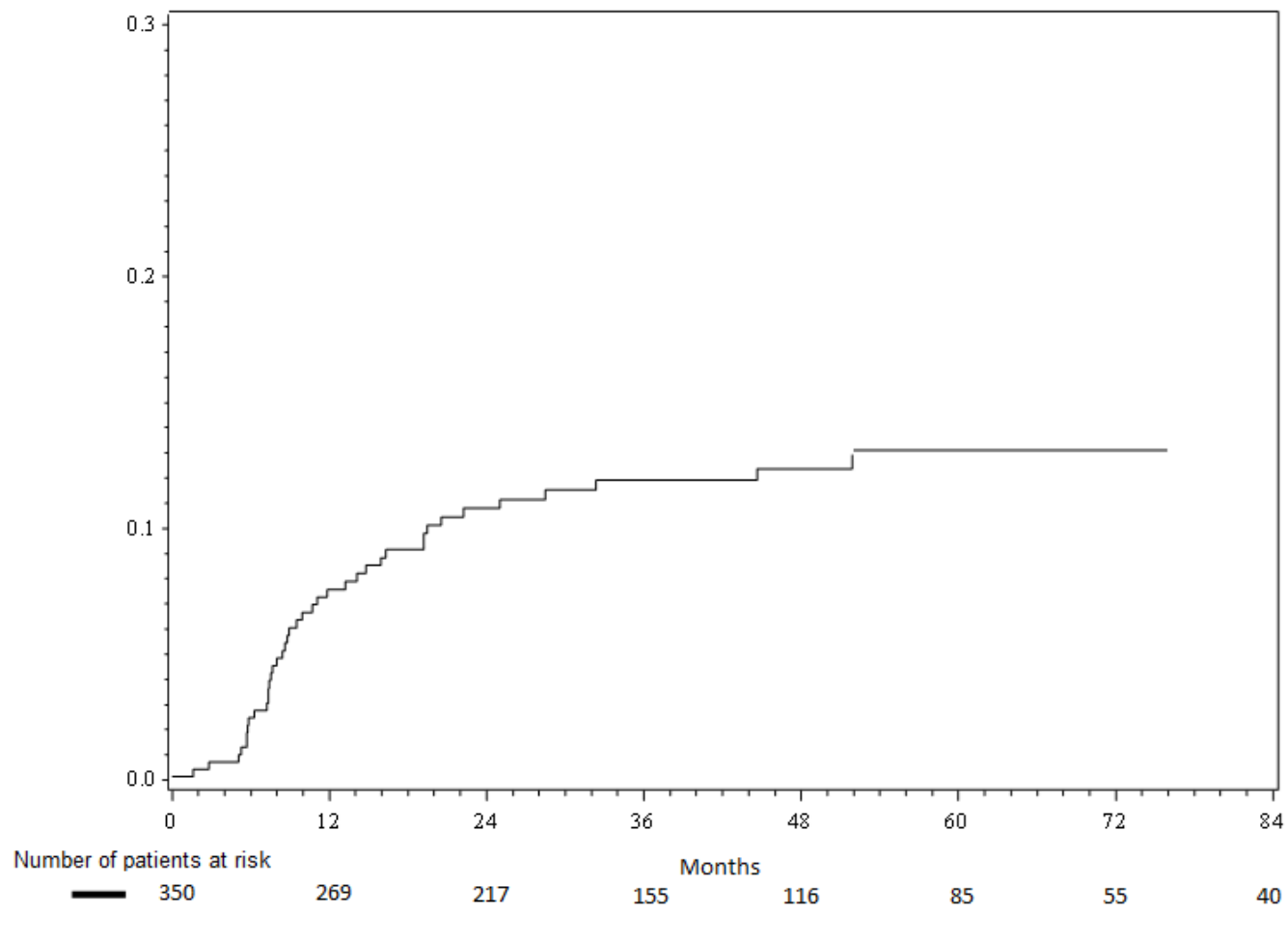
[1] permeation nodule; [2] Left parotide; BI: bilateral irradiation; UI: unilateral irradiation


Local relapses
11
5
7
3
24
14
17
Metastatic relapses
Regional relapses

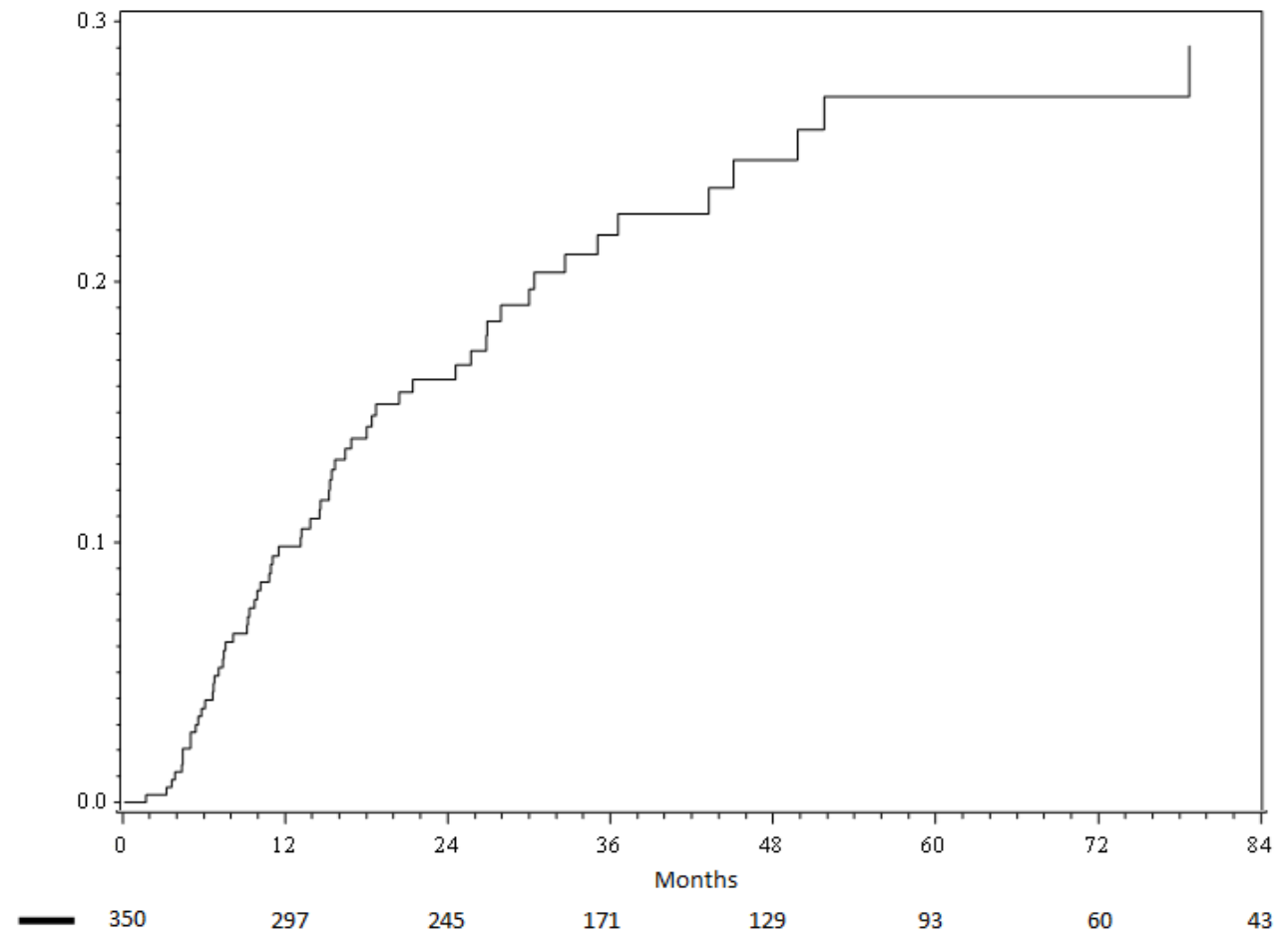
a - Cumulative incidence of local relapse



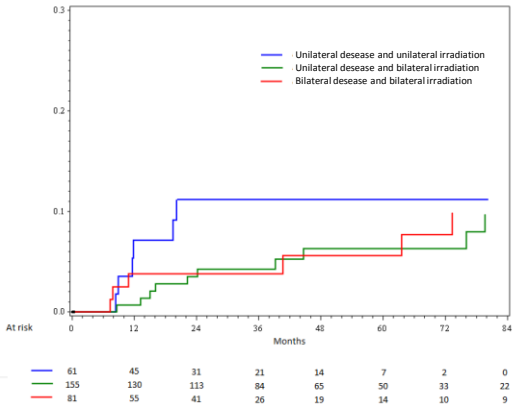
b -Cumulative incidence of regional relapse



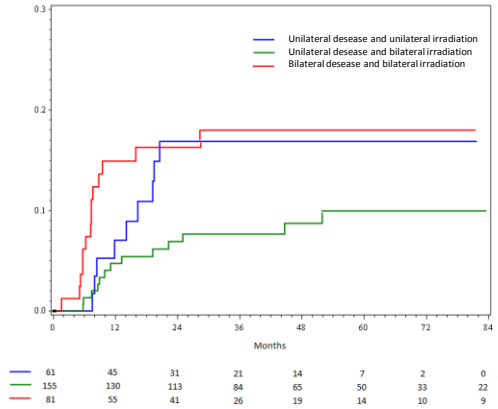
c - Cumulative incidence of CUP specific survival



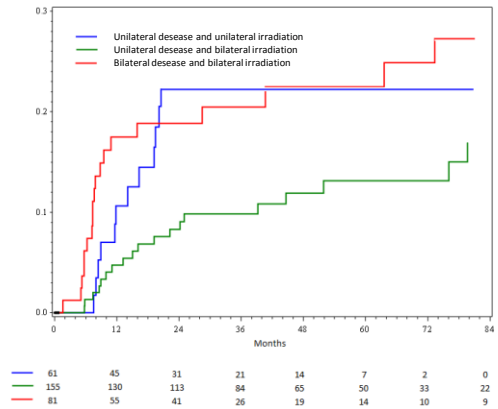
a- Cumulative incidence of local relapse



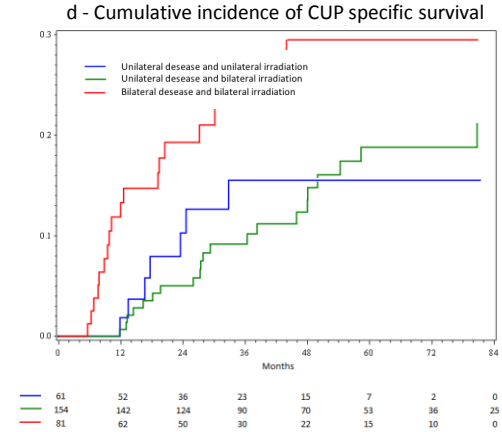
b - Cumulative incidence of regional relapse

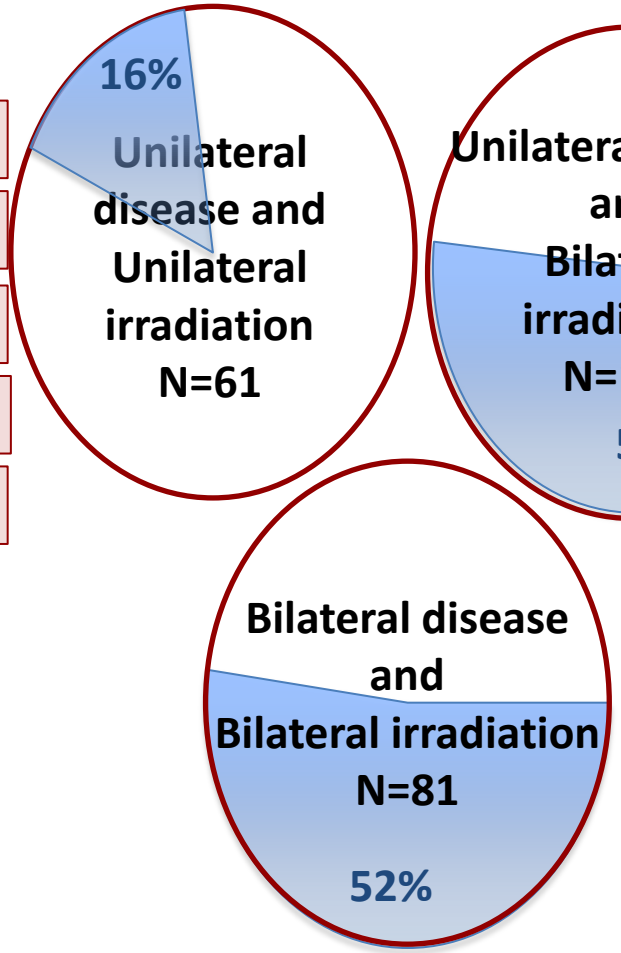


c - Cumulative incidence of locoregional relapse



d - Cumulative incidence of CUP specific survival





Nodal failure*:11 %

Mucosal failure*: 17%

CUP-specific death*: 15%

Acute toxicity Δ : 21%

Late toxicity Δ : 5%

Nodal failure*:4 %

Mucosal failure*: 8%

CUP-specific death*: 9%

Acute toxicity Δ : 38%

Late toxicity Δ : 23%

Nodal failure*: 4%

Mucosal failure*: 18%

CUP-specific death*: 27%

Acute toxicity Δ : 48%

Late toxicity Δ : 25%

Proportion with 3D irradiation: 45 %

Δ At least one toxicity during follow-up

*** Cumulative incidence at 36 months**

Table 6: sides of regional and mucosal relapses

Side of regional relapse for bilateral disease according to radiotherapy target volume

Side of relapse for bilateral disease	Radiotherapy target volume		
	High-risk nodal level	Intermediate risk nodal level	Low risk nodal level
Bilateral	X		X
Bilateral	X	X	X
Bilateral			X
Bilateral	X		X
Unilateral	X		X

Side of regional relapse for unilateral disease according to radiotherapy target volume for ipsilateral and contralateral sides

Side of relapse for unilateral disease	Radiotherapy target volume					
	Ipsilateral			Contralateral		
	High-risk nodal level	Intermediate risk nodal level	Low risk nodal level	High-risk nodal level	Intermediate risk nodal level	Low risk nodal level
Bilateral	X	X				
Bilateral	X	X	X			X
Bilateral	X		X			X
Bilateral	X	X		X	X	
Bilateral	X	X	X			X
Bilateral	X		X			
Contralateral	X		X			X
Contralateral	X					
Contralateral	X		X	X		X
Contralateral	X		X			
Contralateral	missing	missing	missing	missing	missing	missing
Contralateral	X		X			X
Contralateral	X		X			
Ipsilateral	X		X			X
Ipsilateral	X		X			X
Ipsilateral	X	X				X
Ipsilateral	X		X			X
Ipsilateral	X	X	X		X	X
Ipsilateral		X				X
Ipsilateral	X	X				X
Ipsilateral	X		X			
Ipsilateral	X					X
Ipsilateral	X		X			X
Ipsilateral	X		X			X
Ipsilateral	X	X				X
Ipsilateral	X	X	X			X
Ipsilateral	X		X			X
Ipsilateral	missing	missing	missing	missing	missing	missing
Ipsilateral	X					X
Ipsilateral	X		X			
Ipsilateral	missing	missing	missing	missing	missing	missing
Ipsilateral	missing	missing	missing	missing	missing	missing
Ipsilateral	X	X	X		X	X
Ipsilateral	X		X			X
Ipsilateral	X	X	X			

Details of mucosal local relapse

Details of primary relapse												In field relapse
nasopharynx		oropharynx		oral cavity		larynx		hypopharynx		others		
relapse	irradiation	relapse	irradiation	relapse	irradiation	relapse	irradiation	relapse	irradiation	relapse	irradiation	
unspecified												
	BI		BI				BI		BI	X		
	BI		BI				BI		BI	X		
			BI						BI		Yes[1]	
			BI		BI					X		
			UI		UI		UI		UI			
			BI				BI		BI	X		X
unspecified												X
											Yes[2]	X
	BI		BI	X			BI		BI			
	BI		BI	X	BI		BI		BI			
								X				
	BI		BI	X	BI		BI		BI			
	BI		BI	X			BI		BI			
								X				
	BI		BI		BI		BI	X	BI			X
		X	BI				BI	X	BI			X
	BI	X	BI				BI		BI			X
		X										X
X	BI		BI	X	UI		BI		BI			X
	UI		UI		UI		UI	X	UI			X
	BI		BI		BI		BI	X	BI	X		X
	BI	X	BI				UI		UI			X
		X										X
unspecified												
unspecified												

[1] permeation nodule; [2] Left parotide; BI: bilateral irradiation; UI: unilateral irradiation