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Postoperative complications following salvage neck dissection after (chemo) radiotherapy for head and neck squamous cell carcinoma: which patients are at high risk?

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Abstract

Background Salvage neck dissection (ND) is the treatment of choice for residual neck disease after (chemo)radiotherapy for head-and-neck squamous cell carcinoma (HNSCC). Although ND is a relatively safe surgical procedure, several studies have shown that salvage ND will increase the morbidity of (chemo)radiotherapy with possible increase in acute and late toxicity and deterioration of quality-of-life. Therefore, unnecessary salvage ND need to be avoided. However, the available literature could not identify potential groups at higher risk of post-operative complications because of the missing demographic information and the heterogeneity in studies and outcome data. We aim to report on the types, rates, and severity of postoperative complications and to identify groups of patients at high risk of these complications.

Methods Of 908 patients with node-positive HNSCC primarily treated with (chemo)radiotherapy between 2008 and 2022, 130 (14%) underwent salvage ND. Endpoints of the study are the incidence of G ≥ 2 and G3 postoperative complications, identification of risk factors for these complications and the oncologic outcomes.

Results Of all patients who underwent salvage ND, 41% still had vital tumor in ND-specimen (pN+). No G4-5 complications were reported. The incidence of G3 and G ≥ 2(CTCAE.v5) postoperative complications were 18% and 52%, respectively. Events reported as G3 complications were wound infection/dehiscence ($n=9$), fistula ($n=4$), bleeding ($n=4$), tracheotomy ($n=6$), dysphagia ($n=4$), severe pneumonia and septicemia ($n=2$), and frozen shoulder ($n=1$). Seven patients had more than one type of G3 complications. Logistic regression showed that extent of salvage ND, size of the largest node and HPV-negative disease were independent predictors for G ≥ 2 complications. Multivariable analysis showed that G ≥ 2 complications was not associated with worse OS while HPV-negative and N3-disease were independent predictors for worse survival.

Conclusions Of all patients who underwent salvage ND, 41% still had residual neck disease while 52% developed G ≥ 2 and 18% G3 complications. Although OS was not worse in these patients, accurate detection of residual neck disease is essential to spare considerable number of patients from unnecessary salvage ND with its possible

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complications. Patients with lymph nodes larger than 3 cm, HPV-negative disease and those treated by (modified) radical ND were at high risk of G ≥ 2 complications.

Keywords Salvage neck dissection, Complications, HNSCC, Radiotherapy, Chemotherapy

Background

In most patients with node-positive head and neck squamous cell carcinoma (HNSCC) of the pharynx, larynx and unknown primary, the standard of care is radiotherapy, with or without chemotherapy. Patients with (suspected) residual disease (RD) in the neck after primary (chemo)radiotherapy are offered salvage neck dissection (ND).

Until recently, planned ND was often routinely performed particularly in patients with advanced nodal disease or in the presence of extra capsular extension at baseline, as this adjuvant surgical procedure might improve survival outcomes [1, 2]. Therefore, abandoning this concept remained difficult for a long time because of concerns about missing the window of opportunity for cure by delaying or omitting surgery.

The milestone publication by Mehanna et al. [3], significantly changed this paradigm. It demonstrated that PET-guided surveillance both oncologically safe and more cost-effective. As a result, most institutions no longer routinely perform planned ND. This image-guided surveillance has become increasingly adopted in daily clinical practice as the preferred approach. Building on the results of Mehanna et al., our group recently validated the superior performance of FDG-PET/CT for response evaluation after (chemo)radiotherapy in HNSCC. We reported a 89% positive-predictive value (PPV) for identifying pathologic-confirmed residual neck disease in patients who received salvage ND. The negative-predictive value in patients with complete metabolic response was 97.5%, as only 2.5% of these patients developed regional failure later on. Moreover, the increasing use of FDG-PET/CT in the response evaluation pathway in our institution reduced the number of patients exposed to unnecessary salvage ND by 22% with subsequent reduction of the possible complications and morbidity of salvage ND [4].

Although ND is generally considered a relatively safe surgical procedure, several studies have shown that adjuvant ND will add to the morbidity of (chemo)radiotherapy with possible increase in complication and late toxicity rates and possible deterioration of quality-of-life [5–7].

The aim of the current study is to report on types, rates, and severity (grade) of salvage ND complications after (chemo)radiotherapy, to identify subgroups of patients at high risk of these complications, and to investigate the impact of these complications on survival.

Methods

Study population and treatment

Of all patients with histologic-confirmed node-positive HNSCC of the oropharynx, larynx, hypopharynx or unknown primary (n = 908) who were consecutively treated by (chemo)radiation in our institute between 2008 and 2022, 130 patients received salvage ND (14%). These patients form the cohort for the current analysis. Patients with local RD and those received planned ND or ND in the context of late RF were not included in the current analysis. Approval of our institutional review board was obtained (IRBd21-244) for this retrospective study.

Pre-treatment evaluation

Pre-treatment evaluations consisted of a complete medical history and physical examination, including flexible nasolaryngoscopy and when indicated examination under general anesthesia. All patients had ultrasound with fine needle aspiration cytology (FNAC), and head and neck MRI (oropharynx and unknown primary) or CT scan (larynx and hypopharynx) at baseline. In case of locally-advanced disease, any doubt about the nodal status or the presence of distant metastatic disease, FDG-PET/CT was performed.

(Chemo)radiotherapy

Patients were treated with intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT). The radiotherapy dose to the primary tumor and involved node(s) was 70 Gy and to the elective low-risk planning target volume (PTV) was 46 Gy in 23 fractions in case of sequential boost and 54.25 Gy in 35 fractions in case of concomitant boost. Radiotherapy was given in 2 Gy per fraction, 6 fractions a week in case of radiotherapy only and 5 fractions per week in case of chemoradiotherapy. Patients with locally or regionally advanced disease (T3-4, N2c-N3 and those with radiological evidence of extra-capsular extension) were candidates for concurrent cisplatin and patients who were not fit for cisplatin received radiotherapy in combination with Cetuximab.

Follow-up

According to institutional guidelines, the protocol for the response evaluation at 12 weeks includes MRI or CT scan and ultrasound with FNAC, when indicated. In case of any suspicion about the presence of RD at the primary site examination under general anesthesia was performed. In case of any suspicion of RD in the neck on the US-FNAC and/or MRI, FDG-PET/CT was done. FDG-PET/CT was also done instead of MRI in patients with claustrophobia, pacemaker or patient refusal to undergo MRI scan. At our institution, we discuss the results of the investigations done for the response evaluation during the weekly multidisciplinary tumor board meeting. In case of any doubt about the presence of RD in the neck (equivocal FDG uptake or in case of partial metabolic response) patient will receive SND.

The extent and type of the SND will also be discussed in the tumor board meeting. According to our institutional guidelines, patients with solitary nodal metastasis (N1 disease) before treatment and still have one residual node at the response evaluation scan will receive supersecelctive where the only residual node will be removed. Patients with multiple small nodes will receive selective ND, while patients with multiple nodes with other characteristics like node(s) >3 cm, extra-capsular extension or those with N3 disease received (modified)radical ND.

The follow-up was done 3-monthly in the first year, 4-monthly for the second year and 6-monthly thereafter. At each visit, physical examination, including flexible nasolaryngoscopy was performed.

End points

The primary objective of this study was to report on the incidence of grade ≥2 and grade 3 complications after salvage ND. These complications were scored using the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE.v5) [8] and the Clavien-Dindo classifications of surgical complications [9]. The oncologic outcomes in term of regional control (RC), local control (LC), disease-free survival (DFS) and overall survival (OS) were the secondary objectives of the current study.

Statistical analysis

RC and LC were calculated from date of first radiotherapy fraction to the date of regional or local progression, respectively. DFS was calculated from date of first radiotherapy fraction to death from any cause or date of first progression (local, regional, loco-regional or distant progression), whichever occurred first. OS was calculated from date of first radiotherapy fraction to death from any cause, censoring patients who were still alive at last follow-up. Patients who were still alive and did not encounter any progression were censored at last follow-up. Median follow-up time was calculated using the reverse Kaplan–Meier method for OS censoring patients who died. The RC, LC, DFS, and OS were estimated with the Kaplan–Meier method and groups were compared using Log Rank.

The identification of clinical variables associated with higher incidence of grade ≥2 post-salvage ND complications was done using univariable and multivariable logistic regression using bootstrapping with 1000 samples. Cox regression was conducted to identify variables correlated to OS. All tests with a p-value (p) <0.05 were considered statistically significant. All statistical analyses were conducted in SPSS version 29.0 (SPSS Inc, Chicago, IL).

Results

Table 1 shows patients characteristics. The median age is 63 years (range, 42–83) and the median follow-up time was 81 months (range, 5–171). Of the entire group, 78% received (super)selective ND and 22% (modified)radical ND. The median time between end of (chemo)radiotherapy and salvage ND is 16 weeks (range, 12–20). All patients were admitted to the hospital for the salvage ND. The median duration of the admission was 3 days (range, 1–74). Eleven patients (9%) were re-admitted because of complications with median duration of re-admission of 9 days (range, 3–55). Of these patients, 7 patients (8.2%) were treated with chemoradiotherapy and 4 patients (8.8%) were treated with radiotherapy only. The median durations of re-admission of these two groups were 9 and 8 days, respectively. The reasons for re-admission were wound infection and/or dehiscence (n= 5), pneumonia (n= 1), pneumonia and septicemia (n= 1), fistula (n= 1), and combination of reasons (n= 3).

Table 2 shows the incidence of post-operative complications by the type (CTCAE.v5 and Clavien-Dindo classifications) and grade. No grade 4 or 5 complications were reported. Grade 2 and 3 complications according to Clavien-Dindo classifications were reported in 13 (10%) and 18 patients (14%), respectively and 61 patients (47%) had no complication. Twenty-three grade 3 Clavien-Dindo classifications events were reported in 18 patients. These were grade 3 wound infection and/or dehiscence (n = 9), fistula (n= 4), bleeding (n= 4), and tracheotomy (n= 6).

The incidence of grade ≥2 and grade 3 complications according to the CTCAE.v5 were 52% and 18%, respectively and 63 patients (48%) had no postoperative complication according to CTCAE.v5. The most common grade 2 complication was shoulder dysfunction or pain (n= 51, 39%), treated conservatively by analgesics and/or physiotherapy and resolved within 8–14 weeks (median 13 weeks) after salvage ND. Thirty events were reported

Table 1 patient, tumor and treatment demographics ($n = 130$)

	Number (%)
Age; median (range) in years	63 (42–83)
Follow-up time; median (range) in months[a]	81 (5–171)
Admission for salvage ND	130 (100%)
Duration; median (range) in days	3 (1–74)
Re-admission	11 (9%)
Duration; median (range) in days	9 (3–55)
Gender	
Male	103 (79%)
Female	29 (21%)
Site	
OPC	75 (58%)
LC	18 (14%)
HPC	22 (17%)
UP	15 (11%)
T	
Tx (in case of UP)	15 (11%)
T1	20 (15%)
T2	36 (28%)
T3	32 (25%)
T4	27 (21%)
N	
N1	19 (15%)
N2	97 (75%)
N3	14 (10%)
HPV	
Negative	90 (69%)
Positive	40 (31%)
Size of (largest) lymph node	
≤ 3 cm	99 (76%)
> 3 cm	31 (24%)
ECE	
Yes	37 (28%)
No	93 (72%)
Primary treatment	
Radiotherapy alone	45 (35%)
Chemoradiation	85 (65%)
Type of salvage ND	
Superselective ND	17 (13%)
Selective ND	84 (65%)
Radical ND	7 (5%)
Modified radical ND	22 (17%)

Abbreviations: ND neck dissection, *OPC* oropharyngeal cancer, *LC* laryngeal cancer, *HPC* hypopharyngeal cancer, *UP* unknown primary, *HPV* human papilloma virus, *ECE* extra-capsular extension

[a] follow-up time was calculated using the reverse Kaplan–Meier method

Table 2 Postoperative complications according to Clavien Dindo Classification and the CTCAE.v5

	Number (%)
Clavien Dindo classification	
Grade 0	61 (47%)
Grade 1	38 (29%)
Grade 2	13 (10%)
Grade 3	18 (14%)
CTCAE.v5	
Grade 0	63 (48%)
Overall grade ≥ 2 complication	67 (52%)
Any grade 3 complication	23 (18%)
Wound (infection/dehiscence)	13 (10%)
Grade 2 (treated conservatively)	4
Grade 3 (required surgical intervention)	9
Bleeding required surgical intervention	4 (3%)
Grade 2 (treated conservatively)	0
Grade 3 (required surgical intervention)	4
Fistula required surgical intervention	4 (3%)
Grade 2 (treated conservatively)	0
Grade 3 (required surgical intervention)	4
Chyle leak	2 (1.5%)
Grade 2 (treated conservatively)	2
Grade 3 (required surgical intervention)	0
Shoulder problems	52 (40%)
Grade 2	51
Grade 3 (frozen shoulder)	1
Pneumonia	8 (6%)
Grade 2 (treated with antibiotics at out-patient clinic)	6
Grade 3 (required admission for intravenous antibiotics)	2
Tracheotomy (G3)	6 (4.5%)
Duration of tracheotomy; median (range), in days	16 (12–270)
Feeding tube dependency (G3) all	9 (7%)
Feeding tube already exist before salvage ND	5 (4%)
Duration of feeding tube; median (range) in days	180 (150–570)
Feeding tube developed after salvage ND	4 (3%)
Duration of feeding tube; median (range) in days	45 (10–62)

Abbreviations: CTCAE v5 Common Terminology Criteria for Adverse Events Version 5, *ND* neck dissection

as grade 3 (CTCAE.v5) in 23 patients (18%). Of those patients, 7 patients had more than one type of grade 3 complications. Events reported as grade 3 (CTCAE.v5) complications were wound infection and/or dehiscence ($n = 9$), fistula ($n = 4$), bleeding ($n = 4$), tracheotomy ($n = 6$), dysphagia needing feeding tube ($n = 4$), severe pneumonia requiring re-admission and intravenous antibiotics ($n = 2$), and frozen shoulder due to spinal accessory nerve dysfunction ($n = 1$).

Regarding the surgical site complications (wound infection and/or dehiscence, bleeding, fistula, chyle leak), 23 events were reported in 19 patients (14.6%). Of these complications, 17 were major requiring

surgical intervention and 6 were minor and were treated conservatively.

Logistic regression analyses to identify clinical variables associated with a higher incidence of grade ≥2 (CTCAE. v5) post-salvage ND complications showed that patients undergoing (modified) radical ND compared to (super) selective ND were at higher risk for development of grade ≥2 postoperative complications (93% vs. 40%; $p = 0.001$). The same was true for those with the largest lymph node >3 cm (81% vs. 43%; $p = 0.043$) and patients with HPV-negative disease (60% vs. 33%; $p = 0.026$) (Table 3). The rates of grade ≥2 complications in patients treated with radiotherapy only and those treated with chemoradiotherapy were statistically not significant neither in the univariable nor in the multivariable analyses (49% and 53%, respectively, $p = 0.652$).

Of all patients who underwent salvage ND in the current study ($n = 130$), 53 patients (41%) still had vital tumor in the ND-specimen (pN +; true positive RD in the neck) while 59% of patients had no vital tumor in the ND-specimen (pN0). None of the patients with pN + received any adjuvant treatment because of the very short time interval between the primary treatment with (chemo)radiotherapy and the SND. After a median follow-up of 81 months, the RC rates for the entire group were 86% and 82% at 2 and 5 years, respectively. The rates for LC were 79% and 76%, respectively, for DFS were 59% and 43%, respectively, and for OS were 72% and 52%, respectively. The RC rates of patients with RD, compared to those without RD in the neck (pN0) were 76% and 92% at 2 years and 76% and 87% at 5 years (Fig. 1A, $p = 0.087$). The LC rates were 73% and 83% at 2 years and 69% and 81% at 5 years (Fig. 1B, $p = 0.165$). The DFS rates of were 41% and 72% at 2 years and 28% and 53% at 5 years (Fig. 1C, $p = 0.004$) and the OS rates were 59% and 82% at 2 years and 40% and 60% at 5 years (Fig. 1D, $p = 0.026$). The Cox regression analysis for the clinical variable associated with OS showed that only HPV-negative disease and the presence of N3 nodes were associated with worse OS. Although grade ≥2 post-salvage ND complications was significantly predictive for worse OS at the univariable analysis, this variable was not significant any more at the multivariable analysis (Table 4). The OS rates of patients with grade ≥2 complications, compared to those without were 59%, and 87% at 2 years and were 43%, and 62% at 5 years (Fig. 2A, $p = 0.006$) while the rates for patients with grade 3 complications, compared to those without were 51%, and 77% at 2 years and were 45%, and 54% at 5 years (Fig. 2B, $p = 0.154$).

Table 3 Logistic regression analyses for predictive variables for G≥2 CTCAE.v5 postoperative complications

Variables	UVA OR (95% CI); p = value	MVA OR (95% CI); p = value
Age		
≤ 63 (ref)		
> 63	1.21 (0.61–2.51); 0.582	0.69 (0.25–1.71); 0.401
Sex		
Male (ref)		
Female	0.70 (0.28–1.73); 0.421	0.47 (0.08–1.35); 0.183
HPV		
HPV + (ref)		
HPV -	3.11 (1.54–7.89); 0.003	**2.80 (1.15–9.64); 0.026**
Lymph node size		
≤ 3 cm (ref)		
> 3 cm	5.65 (2.38–22.38); < 0.001	**3.31 (1.01–18.25); 0.043**
Chemotherapy		
No (ref)		
Yes	1.18 (0.57–2.47); 0.652	0.87 (0.29–2.35); 0.746
Type salvage ND		
SSND + SND (ref)		
RND + MRND	20.59 (6.54–2,99E + 9); < 0.001	**17.00 (5.29–3.7E + 9); 0.001**

Abbreviations: CTCAE.v5 Common Terminology Criteria for Adverse Events version 5, *UVA* univariable analysis, *MVA* multivariable analysis, *OR* odds ratio, *95%CI* confidence interval, *HPV* human papilloma virus, *ND* neck dissection, *SSND* super-selective ND, *SND* selective ND, *RND* radical ND, *MRND* modified RND

* statistically significant variables in the MVA are indicated in bold

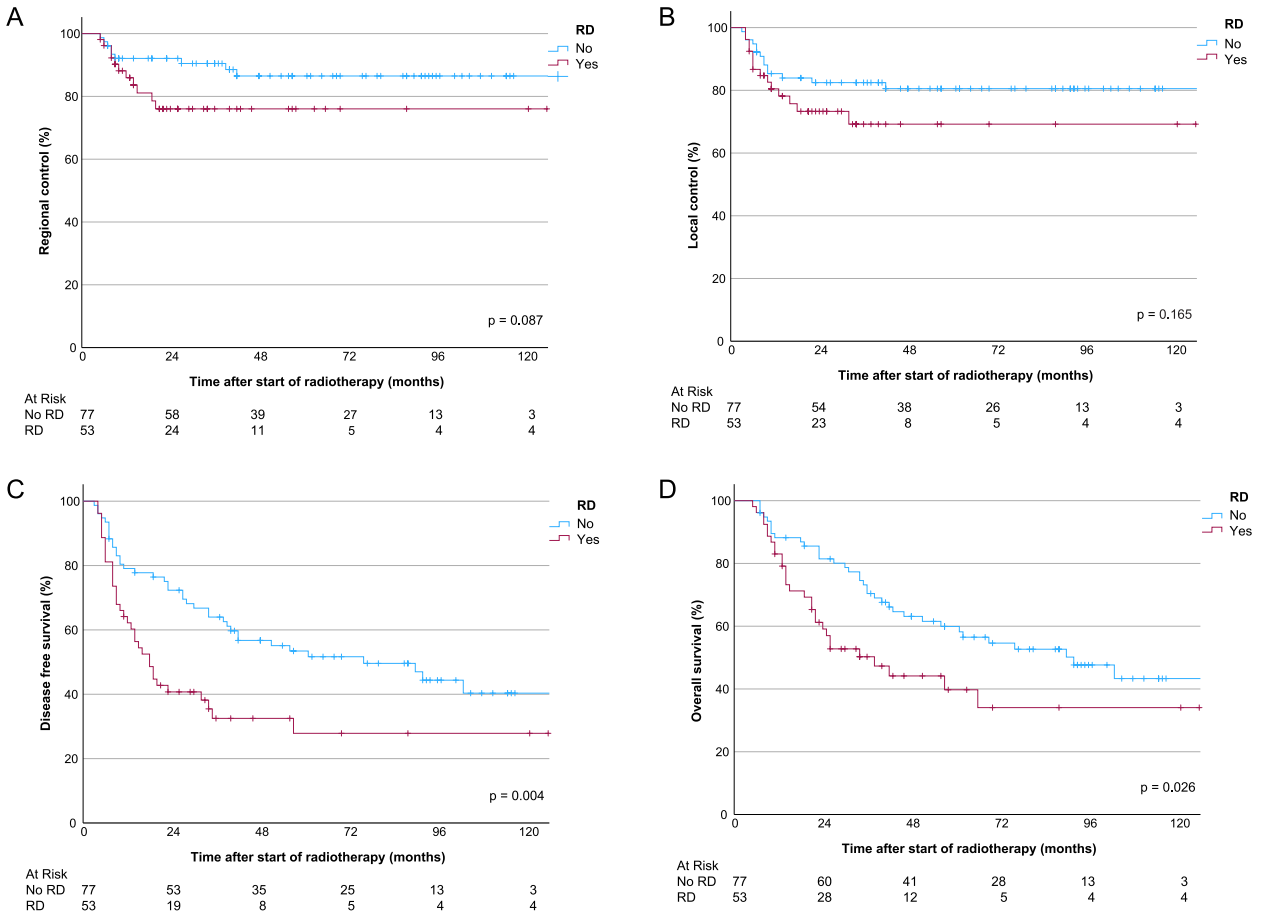

Fig. 1 The Kaplan–Meier curves of regional control (**A**), local control (**B**), disease-free survival (**C**) and overall survival (**D**). in patients with and without residual disease (RD). + censored

Discussion

The current study showed that salvage ND is a safe procedure as no patient experienced grade 4 or 5 complication. However, our study shows that salvage ND is associated with a 52% incidence of grade ≥2 and 18% incidence of grade 3 postoperative complications (CTCAE.v5). The extent of salvage ND, the size of largest lymph node and the HPV-negative status were identified as independent predictors for grade ≥2 postoperative complications (Table 3). Even though patients with grade ≥2 and grade 3 postoperative complications didn't have worse survival (Table 4), careful selection of patients for this surgical procedure is essential to minimize unnecessary NDs and the associated risk of complications. Our group recently published about the accuracy of FDG-PET/CT for the prediction of RD in de neck. Among 908 patients with N+ HNSCC treated in our institution between 2008 and 2022 with (chemo)radiotherapy, the utilization FDG/PET/CT in the response evaluation pathway was significantly increased. Comparing the last 454 with the first 454 patients treated during the study period, significantly more patients in the last study period received FDG-PET/CT (58% vs. 19%, $p < 0.001$). The has resulted in improved accuracy of selecting patients for salvage ND and considerable reduction of patients undergoing unnecessary salvage ND. The number of patients with negative ND was significantly reduced by 22% (from 69% in patients treated in the first period of the study where much less FDG-PET was used to 47% in patients treated in the second period where more and more FDG-PET was used for response evaluation of the neck) [4].

The complication rates after salvage ND reported in the literature showed quite conflicting results and ranged from 3 to 40% [7, 10–14]. A fair comparison between different studies, with regard to the rate and types of complications, is challenging due to the strong variations in patients demographics, the extent of the ND done in these studies, whether the ND was a planned or a salvage

Table 4 Cox regression analyses for predictive variables for OS

Variables	UVA HR (95% CI); *p*-value	MVA HR (95% CI); *p*-value
RD neck		
No (ref)		
Yes	1.74 (1.06–2.85); 0.028	1.44 (0.77–2.68); 0.250
HPV		
HPV + (ref)		
HPV -	5.64 (2.57–12.39); < 0.001	**3.37 (1.40–8.12); 0.007**
Tumor site		
Oropharynx/UP (ref)		
Hypopharynx/larynx	0.45 (0.27–0.74); 0.453	0.64 (0.37–1.11); 0.114
T-stage		
T0-2 (ref)		
T3-4	1.54 (0.95–2.50); 0.083	1.22 (0.72–2.06); 0.465
N-stage		
N1 (ref)		
N2	1.71 (0.73–3.99); 0.217	1.37 (0.58–3.27); 0.473
N3	4.33 (1.62–11.59); 0.003	**3.56 (1.24–10.22); 0.018**
pECE		
No (ref)		
Yes	3.51 (1.88–6.54); < 0.001	1.71 (0.77–3.78); 0.187
G ≥ 2 CTCAE.v5 complications		
No (ref)		
Yes	1.96 (1.19–3.21); 0.008	1.31 (0.75–2.26); 0.342

Abbreviations: OS overall survival, *UVA* univariable analysis, *MVA* multivariable analysis, *HR* hazard ratio, *95%CI* confidence interval, *RD* residual disease, *HPV* human papilloma virus, *UP* unknown primary, *pECE* pathological confirmed extra-capsular extension, *G ≥ 2 CTCAE.v5* grade 2 or higher Common Terminology Criteria for Adverse Events version 5

* statistically significant variables in the MVA are indicated in bold

procedure, which complications are considered and how these are categorized, whether a validated scoring system was used for reporting the toxicity, the thoroughness of chart review and the possible variations in the dose schemes of (chemo)radiotherapy.

Henneman et al. [10] conducted a systemic review on the surgical site complications of post-chemoradiotherapy NDs, analyzing 18 studies included 715 patients and 804 NDs. They reported 117 surgical site complications (14.5%, range 3–29%) with 26.5% of these cases requiring operative intervention. Unfortunately, they could not identify potential groups at higher risk of post-operative complications because of the missing demographic information and the heterogeneity in studies and outcome data. They also stressed the urgent need for standardized toxicity registration. Goguen et al. [11] reported the post-operative complications rates in 105 salvage NDs. The rates of major and minor wound, airway and systemic complications were 8.6%, 14.3%, 8.6%, and 10.5%, respectively. Overall, 28.6% of patients experienced at least one complication, with significantly higher rates observed in patients who underwent salvage ND within 12 weeks after (chemo)radiotherapy; 35.8% and 15.8%, $p = 0.04$. In their publication they also reviewed the literature and included 18 studies ($n = 837$ patients). All these studies reported on major wound complications and only few of them reported on airway ($n = 7$) or systemic complications ($n = 8$). Our results regarding the surgical site complications are in line with those reported in the systemic review of Henneman [10] and the overview of the literature published by Goguen et al. [11].

Regarding the clinical variables associated with a high risk of postoperative complications, the extent of ND was, as reported in other studies [7, 12–17], significantly predictive for grade ≥2 complications. In addition, the size of the largest lymph node >3 cm and HPV-negative disease were also independent predictors for grade ≥2 complications in our study. The finding that HPV-negative status was predictive for a higher incidence of grade ≥2 complications was surprising but intuitively not unexpected as these patients, compared to the HPV + patients, might have a couple of factors (not tested in our study, because these data are not collected) which have negatively influenced these finding. For e.g. these

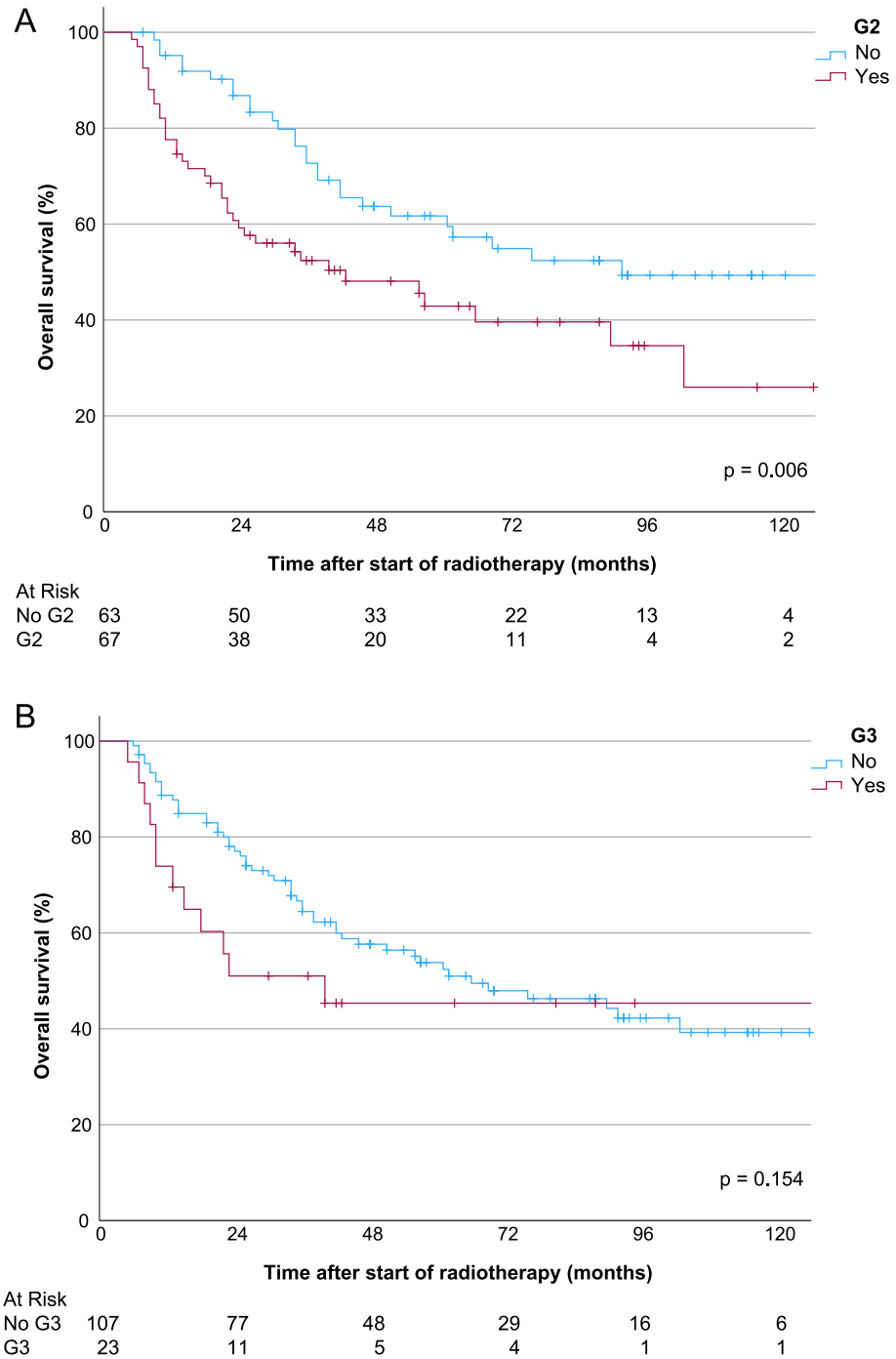

Fig. 2 The Kaplan–Meier curves of overall survival in patients with grade 2 ≥ (**A**) and grade 3 (**B**) postoperative complications. + censored

patients are on average older and might have comorbidities which are increasing the chance of any postoperative complications like use of anti-coagulants increasing the rates of bleeding, COPD and more smokers increasing rates of postoperative pneumonia etc. Consistent with our findings, several other studies have shown that adding chemotherapy to the radiotherapy does not increase the surgical site complications [7, 12, 13]. Intuitively, one might expect higher surgical site complications rates, especially wound complications among patients treated with chemoradiotherapy compared to those treated with radiotherapy only because of reduced vascularity and

fibrosis which might predispose to poor wound healing. A possible explanation is that salvage ND in all of our patients were performed beyond 3 months post-chemoradiotherapy (median time of 16 weeks). In our study, not only the incidence of post-operative complications between these groups was not significantly different but also the number of patient needed re-admission and the duration of re-admission was not significantly different between patients treated with chemoradiotherapy or radiotherapy alone. This might implies that chemoradiotherapy does not necessarily result in costly hospital care, compared to radiotherapy alone.

Despite the differences in postoperative complication rates in the literature, none of the studies have found an association between postoperative complications and worse survival outcomes [11, 12, 16]. In our study, although grade ≥ 2 complications were significantly associated with worse OS in the univariable analysis ($p = 0.008$), in the multivariable analysis only HPV-negative disease and the presence of N3 nodes were associated with worse OS.

The limitations of the current study, including the biases inherent to a retrospective analysis are acknowledged by the authors. The postoperative complications were scored retrospectively using chart review and thoroughly reviewed by two dedicated and experienced head and neck radiation oncologists. However, accurate assessment of less severe complications (grade 1) from the medical records is not reliable because of the subjective nature of this endpoint, likely leading to underreporting. Another drawback of the current study, common to all studies reporting on the post-ND complications, is the lack of patient-reported outcome measures like quality-of-life analysis. Despite these limitations, the present study stands out as one of largest studies to date (130 salvage NDs) reporting on postoperative complications using validated toxicity grading systems (CTCAE.v5 and the Clavien-Dindo classifications) in a homogenous cohort of patients. Notably, all the salvage NDs performed in the current study were done for a possible RD, excluding all planned NDs or NDs in the context of later regional recurrence.

In conclusion, the current study showed that 52% of patients who underwent salvage ND experienced grade ≥ 2 complications, with 18% developing grade 3 complications. The extent of salvage ND, the size of the largest lymph node >3 cm and HPV-negative status were significant predictors for grade ≥ 2 complications. Despite these complications, OS was not worse in patients who experienced postoperative complications. Importantly, 41% of patients who underwent salvage ND had residual vital tumor in the ND- specimen (true pN +), while 59% had complete remission (pN0) after (chemo)radiotherapy for HNSCC. These findings highlight the need for accurate detection and exclusion of residual neck disease to prevent unnecessary salvage ND with its associated risks and complications.

Abbreviations

CT	Computer Tomography
CTCAE.V5	Common Terminology Criteria for Adverse Events, version 5.0
DFS	Disease-Free Survival
FDG-PET	FluoroDeoxyGlucose-PositronEmission Tomography
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human papilloma virus
IMRT	Intensity-Modulated Radiotherapy
LC	Local Control
MRI	Magnetic Resonance Imaging
ND	Neck Dissection
OS	Overall Survival
PPV	Positive Predictive Value
PTV	Planning Target Volume
RC	Regional Control
RD	Residual Disease
SPSS	Statistical Package for Social Sciences
US-FNAC	Ultrasound-Fine Needle Aspiration Cytology
VMAT	Volumetric Modulated Arc Therapy

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Authors' contributions
Study concepts: AN, ZARG, WMK, WHS, LK, MB, AM Study design: AN, ZARG, WMK, WHS, LK, MB, AM Data acquisition: AN, AM, LK, MD, JPB, LS Quality control of data and algorithms: ZARG, AN, MD, EO, AM Data analysis and interpretation: ZARG, AN, MD, EO, WMK, WHS, LK, AM Statistical analysis: ZARG, AN Manuscript preparation: AN, ZARG, AM Manuscript editing: all authors Manuscript review: all authors.

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Data availability
The anonimized datasets used during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Approval was obtained from the institutional Review Board of our institution (IRBd21-244). Patient informed consent was waived by the institutional Review Board of the Dutch Cancer Center/Antoni van Leeuwenhoek due to the retrospective nature of the study. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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