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Systematic review

Up-front neck dissection followed by definitive (chemo)-radiotherapy in head and neck squamous cell carcinoma: Rationale, complications, toxicity rates, and oncological outcomes – A systematic review

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ABSTRACT

Background and purpose: Lymph node metastases of head and neck cancer are considered one of the most negative prognostic factors. While outcomes and feasibility of chemo-radiotherapy ((C)RT) with or without adjuvant planned neck dissection (ND) in organ-preservation treatment strategy have been addressed, the role of ND before (C)RT, called up-front neck dissection (UFND), is not clearly established. This review provides a critical appraisal of UFND. *Material and methods:* Articles were identified with a systematic approach. Outcomes included post-UFND delay of (C)RT, surgical complications, radiation toxicity and oncologic outcome. *Results:* Fifteen studies met inclusion criteria, totaling 607 patients undergoing UFND. Part of the data suggest advantages toward less surgical complications compared with salvage ND, decreased serious acute radiation toxicity and better oncological outcomes when compared with (C)RT alone. The overall heterogeneity of the analyzed data does not allow a meta-analysis that provides high-quality evidence in favor or against UFND. *Conclusions:* Due to lack of well-designed randomized trials, it is difficult to assess the role of UFND in organ-preserving (C)RT setting of head and neck cancer.

Lymph node metastases of head and neck squamous cell carcinoma (HNSCC) are frequent and considered one of the most important prognostic factors, resulting in decreased survival by at least 50% [1]. The successful management of the neck is one of the main pillars in the treatment of HNSCC.

Surgery to the primary tumor with modified radical or radical neck dissection (ND) followed by adjuvant postoperative radiation therapy (RT) with or without concomitant chemotherapy ((C)RT) has been the conventional management of cN2 and cN3 in HNSCC. Therefore, progresses achieved over the last decades have also established radiotherapy (RT) as a means of effective disease control with similar survival rates than the above mentioned surgical strategy. Some advances include altered fractionation RT, intensity-modulated radiotherapy (IMRT), and combination of chemotherapy or non-cytotoxic molecular targeted agents with radiation [2–5]. Single modality approaches with surgery or RT alone is recommended for patients with early-stage tumors (UICC stages I–II), whereas combined modalities, like surgery followed by RT with or without concomitant chemotherapy are generally performed for loco-regionally advanced disease (UICC stages III–IV) [6–8]. In the past two decades, radical CRT has also become a widely accepted treatment alternative to primary surgery, with the advantage of organ-preservation in selected locally advanced HNSCC cases [3].

There seems to be a relative consensus for the management of the neck in cN0–1 patients. In case of surgical management of the primary tumor, elective neck dissection (ND) is performed during the same surgery. In small oral cavity and selected oropharynx cancers, the debate whether to perform elective ND or sentinel lymph node biopsy is ongoing [9–14]. In case of primary RT, elective ND can be considered unnecessary due to excellent nodal control rates. However, with the shift toward organ-preserving strategies, the role of ND is not clearly established for cN2–3 disease. As large and/or hypoxic lymph node metastases are generally less responsive than the primary tumor, planned ND independent of the treatment response or salvage ND only for residual or recurrent nodal disease after (C)RT for advanced HNSCC have been included into these treatment protocols. Stenson et al. reported 35% of ND specimens with microscopic residual tumor in the lymph nodes after CRT [15]. The efficacy of post-RT ND depending

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on the treatment response, after either RT alone or CRT has been reported in a number of series [16–26]. Nevertheless, nodal control rates with and without post-(C)RT planned ND ranged between 55–100% [22–26] and 56–100% [16–21,27], respectively. Additionally, it has been shown in several studies that a ND after (C)RT increases the risk of delayed wound healing and other postoperative complications. Local and systemic complication rates after ND of the previously irradiated region varied from 5% to 77% [28–32], with severe late grade 3 toxicity reported as high as 55% [28,33].

In attempt to decrease the risk of postoperative complications and to increase a better regional control, planned ND without surgery to the primary tumor before (C)RT in patients with advanced HNSCC has been employed in organ-preservation strategy. The so called up-front ND (UFND) is currently less known and performed [6], but confers the advantages of avoiding adjuvant surgery on a previously irradiated neck as well as the removal of hypoxic tissues and bulky nodal metastases, which may be less responsive to (C)RT and possibly associated to an increased risk of distant metastases [34–36]. Satisfying control and postoperative complication rates with UFND, along with minimal delay of definitive treatment, have been reported previously [31,37–42]. Despite the good results of UFND, many authors consider this approach as a redundant strategy, since definitive (C)RT will take place to the primary tumor site and the neck [25,43]. Still, questions about sequencing and/or exact requirements for ND in organ-preserving concomitant CRT strategies remain unanswered.

We hereby performed a systematic review on UFND in HNSCC. This work has the purpose to present treatment-related complications, toxicity rates and oncological outcomes as well to discuss the current role of UFND.

Materials and methods

Identification of studies and data extraction

Two independent authors (OE and LN) conducted a systematic literature search in MEDLINE and SCOPUS databases without any constraint for the starting date until December 2013. In addition, meeting abstracts were searched in congress books of the American Head and Neck Society, the American Society for Radiation Oncology, the European Society for Radiation Oncology, the European Cancer Congress and the American Society of Clinical Oncology between 2011 and 2013. The search terms used implementing Boolean algorithms were: "*Head and Neck Neoplasms*"*[Mesh], split, therapy, up-front, upfront, planned, before, followed by, neck, dissect* and thyroid* (for exclusion)*. For Scopus and abstract books the following query terms were used: *neck, dissect*, split, therapy, upfront, up-front, planned, before, followed by, and thyroid* (for exclusion)* within the category of medicine. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were followed to document details on the search strategy and selection processes [44].

Inclusion criteria

We included publications concerning patients with HNSCC of oral cavity, oropharynx, hypopharynx and larynx. Studies had to contain patients treated with UFND before definitive RT with or without concomitant chemotherapy to the unresected primary tumor and lymphatic levels according to clinical and pathological findings. At least one of the following endpoints had to be reported for the UFND patients: regional control, loco-regional control (LRC), disease-free survival (DFS), overall survival (OS), post-operative complications or RT toxicity. Due to the sparsity of data we did not limit our search to studies necessarily having a comparator group or a specific design. Treatment strategies with exclusively neoadjuvant/induction chemotherapy before surgery were excluded.

Extracted data were recorded into standardized spread sheets according to the following parameters: author, year of publication, study period, study design, follow-up time, mean age of patients, number of treatment arms/groups, total number of patients, number of patients treated with UFND, types of UFND, RT technique and dose, chemotherapy regimen used (if any), disease and patient characteristics, delay of definitive treatment after UFND, explanation of the additional arm(s) (if any), patterns of failure (primary tumor and/or neck), LRC rate, OS, DFS, distant metastasis-free survival (DMFS), disease-specific survival (DSS), RT dose reduction secondary to UFND, post-operative complications, and RT toxicity.

Results

Search results

The literature search yielded a total of 1131 articles and abstracts. Only 15 of those met all inclusion criteria and were considered for final analysis [31,37–42,45–52]. A flowchart detailing the number of screened, included and excluded articles, as well as the reasons for exclusion is provided in Fig. 1. All included studies were published in the last 25 years. No articles were excluded because of language.

Patients' characteristics and study designs (Tables 1 and 2)

The total number of patients reported with UFND was 607. Patients in the reported study cohorts were treated between 1972 and 2010. Of the 15 studies, 13 were retrospective [31,37–42,45–48,51,52] and 2 were prospective [49,50]. Patients were allocated to a single arm in 9 studies (UFND only) whereas 6

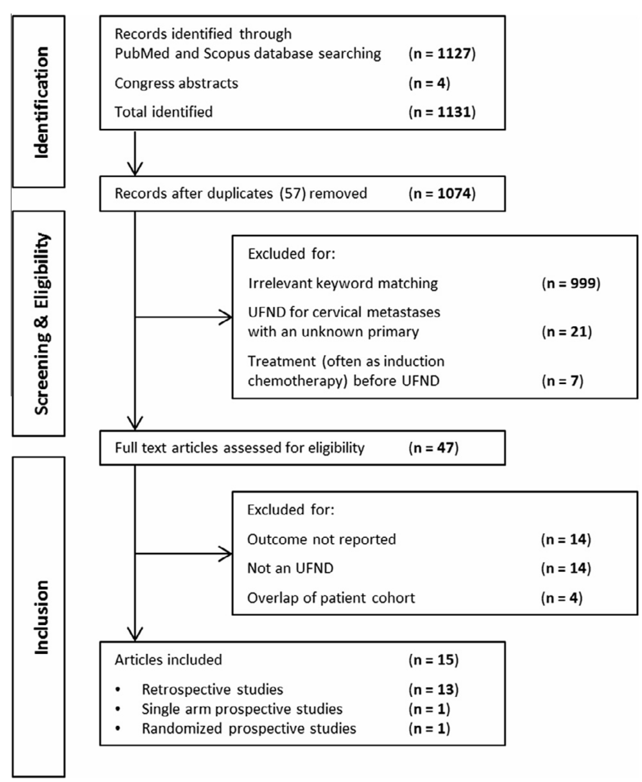

Fig. 1. PRISMA flowchart with identified, screened and included articles. PRISMA: preferred reporting items for systematic reviews and meta-analyses, UFND: up-front neck dissection.

Table 1
Patients' characteristics and study design.

Author & year	Study type	Study period	Follow-up (years)	Age (range)	Arms/groups	N. of UFND patients (total)	UFND type	RT technique	Dose to neck (Gy)	cCX
Brugere [45] 1991	R	1984–1987	⩾5 (m.)	m.: 58 (35–85)	3	65 (313)	61 RND, 4 MRND	nor	nor	No
Byers [38] 1992	R	1972–1988	⩾2 (m.)	md.: 61 (43–78)	1	35 (35)	"functional ND"	nor	⩾50	No
Verschuur [46] 1996	R	1985–1992	3.9 (m.)	m.: 52.9 (32–78)	1	15 (15)	13 RND, 2 MRND	nor	66–80	No
Peters [42] 1996	R	1984–1993	3.3 (md.)	md.: 59 (34–83)	3	17 (100)	17 MRND	2D	54	No
Allal [47] 1999	R	1991–1996	2.6 (md.)	m.: 57 (nor)	2	24 (41)	23 RND, 1 MRND	2D	⩾50.4	6 cases
Smeele [48] 2000	R	1988–1998	2.6 (m.)	m.: 64 (40–87)	1	32 (37)*	25 RND, 7 MRND	nor	⩾60	No
Carinci [49] 2001	P rando-mized	1991–1997	⩾2 (m.)	md.: 62 (44–77)	2	23 (54)	2 RND, 21 "functional ND"	nor	nor	Cisplatin + 5FU
Reddy [39] 2005	R	1996–2003	3.2 (m.)	md.: 55	1	16 (16)	1 RND, 13 MRND, 2 SND	2D	50–60	"if necessary"
D'Cruz [50] 2006	P single arm	1993–2003	2.1 (md.)	md.: 56 (39–73)	1	52 (52)	RND and MRND	2D	46–60	No
Cupino [40] 2007	R	2000–2003	3 (md.)	md.: 55 (41–75)	1	25 (25)	SND	3DCRT + IMRT	50–66	Weekly paclitaxel and/or platinum
Prades [41] 2008	R	1996–2002	⩾1.5 (m.)	m.: 54 (35–70)	1	76 (76)	19 RND, 42 MRND, 1 SND, 4 bilateral ND	nor	50–75	Mixed in time
Paximadis [37] 2012	R	2000–2009	3.9 (md.)	m.: 53 (40–74)	1	55 (55)	11 RND, 44 MRND	3DCRT + IMRT	50–66	Platinum or cetuximab
Liu [31] 2012	R	1999–2005	4.1 (md.)	m.: 56 (39–76)	2	46 (85)	29 MRND, 12 RND, 5 bilateral ND	2D	50–72	24 cases with cisplatin after 2003 (induction (n = 20) before 2003)
Al-Mamgani [51] 2013	R	1996–2010	2.8 (md.)	md.: 60 (38–87)	2	32 (135)	4 RND, 15 MRND, 13 SND	3DCRT + IMRT	46–66	9 cases with cisplatin
Shenoy [52] 2013	R	1991–2008	2 (md.)	md.: 54 (32–70)	1	94 (109)*	55 RND, 39 MRND	"RT with or without [planning] CT"	60–66	24 cases (mostly N3) weekly cisplatin

cCX: concomitant chemotherapy, CT: Computed Tomography, IMRT: Intensity modulated radiotherapy, m.: mean, md.: median, MRND: modified radical neck dissection, ND: neck dissection, nor: not reported, P: prospective, R: retrospective, RND: radical neck dissection, RT: radiotherapy, SND: selective neck dissection, UFND: up-front neck dissection, 2DRT: two-dimensional conventional radiotherapy, 3DCRT: three-dimensional conformal radiotherapy, 5FU: 5-Fluorouracil.

* Remaining patients either not irradiated, did not complete treatment or irradiated for palliative intention.

Table 2
Description of studies with more than one arm.

Author & year	Description of additional arms other than UFND	Differences regarding characteristics or treatment
Brugere [45] 1991	2nd ($n = 53$): partial laryngectomy + ND + adjuvant RT 3rd ($n = 195$): RT without planned ND	nod
Peters [42] 1996	2nd ($n = 75$): induction chemotherapy ($n = 6$) + RT without planned ND 3rd ($n = 8$): up-front single node excision	nor
Allal [47] 1999	2nd ($n = 17$): RT ± concomitant chemotherapy ($n = 8$) without planned ND	Similar median doses to involved nodes (69.9 Gy), with ranges of 56.4–70.4 Gy and 67.5 to 69.9 Gy in groups with and without UFND, respectively
Carinci [49] 2001	2nd ($n = 31$): CRT with cisplatin + 5FU without planned ND	CRT alone arm contained 6 patients with cN3 disease whereas UFND + CRT had none
Liu [31] 2012	2nd ($n = 39$): induction chemotherapy ($n = 19$) + CRT with different schedules without planned ND	nod
Al-Mamgani [51] 2013	2nd ($n = 103$): RT ± concomitant cisplatin (77%) without planned ND	More patients in group 2 had advanced disease (T3–4) compared to group 1 ($p = 0.007$) More patients in group 2 were treated with concomitant cisplatin (77% vs 28%, $p < 0.0001$)

CR: complete response, CRT: concomitant chemoradiotherapy, ND: neck dissection, nod: no difference, nor: not reported, RT: radiotherapy, UFND: up-front neck dissection, 5FU: 5-Fluorouracil.

articles described more than one arm (Tables 1 and 2). The cohort sizes of patients with UFND ranged from 15 to 94 patients. In the studies with more than one arm, the percentage of patients in the UFND cohort ranged from 17% to 86%. Treatment modalities for groups other than UFND had extreme variations through studies. Groups/arms other than UFND and (C)RT contained surgery to the primary tumor and ND with the addition of post-operative RT in one study [45] and (C)RT alone without planned ND in the remaining studies (Table 2) [31,42,45,49,51]. Salvage NDs were performed in case of less than complete clinical response or recurrence. One study [42] included a third group with 8 additional patients treated with single nodal excision prior to RT.

The types of UFND were modified radical and radical ND in the majority of cases. RT technique was not described in 7 studies [38,41,45,46,48,49,52]. Two-dimensional conventional RT was reported in 5 studies [31,39,42,47,50]. Three-dimensional conformal and IMRT techniques were described in 3 studies [37,40,51]. Most of the study cohorts were treated in an era when the use of concomitant chemotherapy was not established as standard (published until 2001). Before this date, only Allal et al. (1999) treated some patients with concomitant CRT [47]. Except for one study [50], concomitant CRT was preferred in all studies published after 2001. Descriptive data of follow-up time varied across publications (e.g. mean, median, "at least"), but all studies had at least 1.5 year follow-up (Table 1).

Disease characteristics (Supplementary Table 1)

The distribution of disease characteristics varied markedly among the studies. Some authors only reported the general characteristics of the whole cohort without the details of patients treated with UFND. Most common primary site was hypopharynx (45%), followed by oropharynx (38%), larynx (16%) and oral cavity (<1%). All studies included patients having nodal positive necks (cN1–3) except 3 articles [37,41,49] containing 1–5 cN0 cases (2–22%). The majority of the cases had cN2–3, stage IVA/B disease. However, it should be noted that different versions of the AJCC/UICC for TNM staging were used depending on the publication date. HNSCC was the only histology with the exception of 3 undifferentiated carcinomas of tonsil (2 patients) and piriform sinus (1 patient) included in one study [48].

Delay of (chemo)-radiotherapy due to UFND and postoperative complications (Supplementary Table 2)

Time interval between UFND and (C)RT was reported in 10 articles [31,37,40,41,46–48,50–52], some reporting median, some mean values. It can be interpreted that (C)RT began around the 4th week after the UFND (range: 10–75 days). Two authors assessed the impact of RT delay on oncological outcome. Byers et al. [38] found that a delay greater than 14 days to start RT following UFND was significantly associated with inferior overall survival ($p = 0.01$, only Kaplan–Meier curves provided), whereas Smeele et al. [48] could not show any significant impact on outcome.

When details were provided in the article, surgery-related complications due to UFND were categorized as minor (wound complications not requiring an intervention or causing any permanent damage to structures) or major (local problems requiring surgical intervention, systemic complications requiring intensive care or causing permanent loss of function). Post-UFND complications were reported in 13 studies. Eight of them reported total post-operative complication rates of less than 10% [31,37,38,41,42,46,50,51] whereas the remaining 5 studies showed complications between 12% and 37% [39,40,47,48,52]. Post-operative complications were assessed in 2 studies comparing strategies with and without UFND [31,42]. Surgical complications were reported to be lower after UFND (8%) compared to salvage ND for nodal persistence/recurrence (12.5%) by Peters et al. [42]. According to Liu et al. [31] complication rates after UFND were 7% vs. 77% (54% major complications, half of them requiring pectoral major myocutaneous flap and the other half requiring additional surgery) after salvage ND for nodal persistence/recurrence. Unfortunately, no statistical analyses were performed in these articles and it is not clearly reported whether the salvage surgery was only performed for isolated neck failure or included also patients with surgery for synchronous loco-regional relapses, which would explain the reason for much higher complication rates.

Toxicity after (chemo)-radiotherapy (Supplementary Table 3)

(C)RT toxicities were poorly reported. Skin and soft tissue toxicities in the neck region were rarely described separately. Six authors [31,39,41,45,49,50] did not mention toxicity and in the other 9 articles [37,38,40,42,46–48,51,52] different scales or subjective evaluations were used. Percentage of "serious" or grade $\geqslant 3$ toxicities ranged from 0% to 80% for acute [40,46,47,51,52] and 0–20% for late toxicities [37,38,40,42,46–48,51] among cases treated with UFND strategy. Two authors compared grade $\geqslant 3$ toxicities among the groups treated with and without UFND: Allal et al. [47] found no significant differences for acute (80% vs. 86%) and late toxicities (8% vs. 6%), whereas Al-Mamgani [51] reported significantly higher grade 3 acute toxicity in patients treated with

Table 3
Oncological outcome.

UFND + (chemo)-radiotherapy*									
Author & year	Local control	Isolated nodal control	Regional control	LRC	DMFS	DFS	DSS	OS	Differences to other arms
Brugere [51] 1991	91%	95%	86% at 3 y.	nor	62%	nor	nor	md.: 19 mth.	Isolated nodal control: 95% in UFND, 92% in post-operative RT and 80% in RT only group ($p = 0.04$) Nodal control at 3 y.: 86% in UFND and post-operative RT groups, 62% in RT only group ($p = 0.02$) No sign. difference in OS or distant metastasis among the three groups Post-operative RT group had better md. survival in supraglottic cancer: 40 mth. vs 18 mth. (UFND) vs 17 mth. (RT only group) ($p = 0.03$)
Byers [38] 1992	69% at 2 y.	89% at 2 y.	86% at 2 y.	57% at 2 y.	nor	51% at 5 y.	nor	55% at 5 y.	–
Verschuur [46] 1996	80%	100%	100%	80%	73%	nor	nor	73% at 3 y. 60% at 5 y.	–
Peters [42] 1996	nor	82%	76% (80% at 2 and 3 y.)	nor	nor	nor	nor	nor	Isolated nodal control: 82% in UFND, 96% in the RT only group (no statistical comparison)
Allal [47] 1999	81% at 3 y.	92% at 3 y.	78% at 3 y.	73% at 3 y.	nor	60% at 3 y.	nor	37% at 3 y.	No sign. differences in local (81% with UFND vs 75% with (C)RT, $p = 0.97$) or loco-regional control (73% with UFND vs 55%, $p = 0.5$) between groups
Smeele [48] 2000	59% at 2 y.	nor	78% at 2 y.	43% at 2 y.	45% at 2 y.	nor	49% at 31 mth.	35% at 2 y.	–
Carinci [49] 2001	nor	nor	nor	nor	nor	nor	52% at 2 y. 26% at 5 y.	nor	In UFND and CRT alone arms, DSS in 2 and 5 y. were 52% and 26% vs 29% and 0% respectively. CRT alone arm had worse DSS (OR: 1.96 with 95% CI: 1.04–3.7, $p = 0.037$)
Reddy [39] 2005	100%	94%	94%	94%	-	94%	nor	100%	–
D'Cruz [50] 2006	92%	88%	87%	80% at 5 y.	88%	54% at 5 y.	nor	80% at 2 and 3 y. 60% at 5 y.	–
Cupino [40] 2007	92%	100%	100%	95% at 2 y.	91% at 2 y.	88% at 2 y. 75% at 3 y.	nor	92% at 2 and 3 y.	–
Prades [41] 2008	84%	94%	89%	82% at 2 y.	nor	nor	67% at 2 y.	43% at 2 y.	–
Paximadis [37] 2012	87%	100%	96%	87%	78%	65% at 5 y.	nor	71% at 5 y.	–
Liu [31] 2012	78%	91%	86%	70%	96% at 5 y.	nor	46% at 5 y.	43% at 5 y.	Regional control better in UFND arm than CRT alone (86% vs 66% $p = 0.02$)
Al-Mamgani [51] 2013	84% at 3 y.	nor	92% at 3 y.	nor	80% at 3 y.	64% at 3 y.	78% at 3 y.	66% at 3 y.	Better 3 y. OS (66% vs 42%, $p = 0.04$) and DSS (78% vs 56%, $p = 0.03$) with UFND compared to (C)RT alone in univariate analysis. However only T stage remained as a significant factor in multivariate analysis
Shenoy [52] 2013	84%	nor	65%	nor	81%	70% at 5 y.	nor	61% at 5 y.	–

CRT: concomitant chemoradiotherapy, DFS: disease-free survival, DMFS: distant metastasis-free survival, DSS: disease-specific survival, LRC: loco-regional control, md.: median, mth.: months, nor: not reported, OS: overall survival, RT: radiotherapy, UFND: up-front neck dissection, y.: years, "–": only one arm study.

* Rates without any specified time point indicate the crude event rates until last follow-up.

(C)RT alone (72% vs. 50%, $p = 0.02$). However in the latter, (C)RT alone group consisted of patients with more advanced stage disease requiring larger RT fields compared to patients who underwent UFND prior to (C)RT. Additionally, Peters et al. [42] reported fibrosis rates of 20% and 24% with and without UFND, but no statistical comparison was performed.

Oncological outcome (Table 3)

Outcome endpoints were not reported homogenously. Some reported failure/survival rates at 2, 3 and/or 5 years and some reported crude rates at the time of last follow-up. Oncological outcomes of patients undergoing (C)RT with and without previous UFND were compared in 5 retrospective studies [31,42,45,47,51]. The French Head and Neck Study Group (Brugere J) [45] and Liu et al. [31] showed a significant positive impact of UFND on regional control (86% vs. 62%, $p = 0.02$ and 86% vs. 66%, $p = 0.02$, respectively), and Al-Mamgani et al. [51] described significant positive impact on survival of the group with UFND in univariate (66% vs. 42%, 3-years survival, $p = 0.03$) but not in multivariate analysis. However it should be noted that in the study by Liu et al. [31] approximately half of the patients in each arm were treated with induction chemotherapy before UFND and RT and the outcome of these subgroups were not separately reported. Peters et al. [42] (isolated nodal control: 82% vs. 96%) and Allal et al. [47] (local control: 81% vs. 75%, $p = 0.97$ and loco-regional control: 73% vs. 55%, $p = 0.52$) reported no statistically significant difference in the outcome comparing patients treated with and without UFND. In addition to those retrospective studies showing better oncological outcome in patients undergoing UFND, the sole prospective randomized study of Carinci et al. [49] confirmed the significant positive impact on survival in UFND arm (DSS: 52% vs. 29% 2-years and 29% vs. 0% 5-years; Odds ratio for DSS: 1.96 95% CI: 1.04–3.7, $p = 0.037$).

Discussion

Treatment of advanced loco-regional HNSCC still remains a challenge and the control of lymph node metastases is a problem of major importance. Several reasons can be advanced for this, including increased tumor load, hypoxia, or intrinsic biological features of lymph node metastases. All these can contribute to radioresistance. Therefore, surgical removal of large nodal disease before or after definitive (C)RT should hypothetically lead to a better oncological outcome, and in some studies, patients with UFND displayed improved nodal control, DSS and OS compared with those undergoing (C)RT alone. Our systematic review also provides clues that UFND treatment strategy as a part of organ-preservation protocols has less complications than salvage ND for isolated neck persistence/recurrence [42]. Patients treated with UFND and (C)RT seem to have less serious acute toxicity than those treated with (C) RT alone. On the other hand, even if toxicity and complication rates are actually decreased with UFND, it has to be considered that surgery carries its own risks and costs. In other words, a careful 'number needed-to-treat' and a well-balanced cost-benefit analysis has to be performed.

Previous high-dose radiation delivered to the neck considerably increases the risk of postoperative complications after ND [29,53]. Soft tissue fibrosis and decreased vascularization are responsible for an increased risk of wound dehiscenses, infections, impaired hemostasis and higher vulnerability of large vessels leading to ruptures of the carotid artery in worst case. Of the articles included in this analysis, only two compared the postoperative complications between patients treated with UFND and those with salvage ND in case of oncological failure, showing a much higher complication rate in the latter group [31,42]. Due to the fact that there were only two UFND studies comparing the surgical morbidity between these two strategies, we looked for other articles in the literature which reported complications with planned ND and salvage ND for isolated nodal recurrence after (C)RT. Complications after planned ND which is performed after (C)RT ranged from 5% to 38% [15,22, 28–30,54–62], and among articles which report detailed information, the rates of minor and major complications were between 2% and 16% and 0% and 20%, respectively [15,16,22,28,30,54,55,57,58,60,61,63–65]. These results are similar to the complication rates after UFND. Studies reporting complication rates of salvage ND explicitly describing postoperative morbidity after surgery for isolated neck recurrences without including the results of patients who underwent combined surgery for loco-regional relapse or who underwent salvage ND on initially operated and/or non-irradiated patients are rare. In studies where salvage ND was only performed for isolated neck failures (without synchronous failures of the primary), complication rates ranged from 4% to 69%, and the rates of major complications varied between 4% and 54% with a postoperative mortality rate reaching 6% [32,66–69]. The rate of complications after salvage ND seems to be higher than after UFND. However, it should be noted that the percentages of postoperative complications reflect the whole population of patients who were treated with the UFND approach, whereas the rates of complications after planned ND or salvage ND belong to a selected group of cases, because these operations are not performed if the primary tumor does not respond to (C)RT and is inoperable. This makes a comparison with UFND cohorts questionable.

Where one advantage of UFND is to avoid operating and re-irradiating a neck after a full course of (C)RT in case of persistent or recurrent nodal disease, another advantage may be the obtained level-specific mapping of nodal disease (macrometastases, extracapsular spread, presence of micrometastases) and subsequently allowing the dose and volume of RT to be tailored based on these findings. Depending on nodal disease extent, patients may receive a lower dose to the neck after UFND which removes gross disease, compared to the higher dose given to all patients primarily treated with (C)RT. Reducing the dose to the irradiated neck levels after UFND knowing the nodal status may decrease the acute and late toxicity. Unfortunately, no study focused specifically on this subject, and therefore it is not possible to argue for a clear benefit regarding decreased toxicity due to dose and volume reduction in cases of UFND. However, in spite of a lower dose (or no dose at all in case of a down-staged pN0/1 hemi-neck, without extracapsular extension), the RT volumes in the post-operative neck may on the contrary be slightly larger when compared to non-operated neck levels, especially in case of extracapsular spread. The question of whether a higher dose of RT alone or an UFND combined with a lower radiation dose is more toxic, remains unanswered. Among 2 articles in which a comparison of (C)RT with or without UFND was done, only Al-Mamgani et al. [51] showed a statistically significant lower rate of acute grade $\geqslant 3$ toxicity with UFND strategy. Grade $\geqslant 3$ chronic toxicity rate compared in 2 retrospective studies was similar between patient arms with and without UFND [47,51]. Series of (C)RT without UFND reported grade $\geqslant 3$ chronic toxicity between 0% and 55% which seems to be numerically higher than reported in the UFND patients, but any direct comparison is not possible [17,30,31,33,37–42,45–52,56,58,64,70–74]. Progress in the RT techniques and better understanding of dosimetric parameters of the organs at risk may positively affect toxicity related outcomes and decrease the post-(C)RT related toxicity in patients both with and without UFND [75].

It is generally accepted that, due to the very low probability of nodal persistence and the morbidity associated with ND, any planned ND before or after (C)RT in organ-preservation protocols is usually not considered for cN0–1 disease [6,25,65,76–79]. On the other edge of the spectrum, the risk of residual and viable tumor after CRT is substantial for cN2–3 disease and positively correlated to N stage and nodal size [28,80–82]. Additionally, pathologically proven viable tumor cells in lymph nodes after CRT are related with poorer survival [24,65]. In the planned ND series, Cho et al. showed that 30% of the patients had persistent or recurrent nodal disease after CRT, and even if complete clinical response was achieved, Cannady et al. reported a 13.8% rate of histologically positive ND specimens [80,81]. Thariat et al. showed that patients with lymph nodes bigger than 3 cm had greater than 35% isolated and overall neck recurrences within 5 years [25]. Especially prior to the introduction of CRT, combinations of UFND or planned ND and RT for cN2–3 disease were widely established treatment strategies [6].

Concerning oncological outcomes, there were only 2 prospective trials found in our review. Carinci et al. [49] reported results with two small randomized arms: (1) UFND followed by CRT and (2) CRT alone without planned ND. Only DSS was reported (2- and 5-years: 52% and 26% vs. 29% and 0%, respectively) with univariate Cox regression analysis favoring the UFND cohort ($p < 0.05$). While promising, this study presents several limitations that impose careful interpretations of these results: (1) randomization methodology and stratification factors not reported; (2) non-adherence to initial inclusion criteria (not only locally-advanced HNSCC were included); (3) RT dose to the neck not reported; (4) lack of relevant outcome measures, mainly local, regional, and distant control, as well as CRT toxicity rates.

D'Cruz et al. [50] reported the second prospective trial, a single-arm study which included early local (cT1-2) but regionally advanced (cN2a/b) tumors. The patients received 2-dimensional RT with doses to the primary tumor $\geqslant$66 Gy and doses of 46–60 Gy to the neck. Patients did not receive concomitant chemotherapy. This study emphasized the feasibility of UFND with an 88% isolated regional control and LRC of 80% at 5 years. Of the remaining 13 retrospective studies, 5 contained more than one study arm, none including a planned ND strategy. Concerning the studies comparing UFND followed by (C)RT vs. (C)RT alone, 3 studies (Brugere [45], Liu et al. [31], Al-Mamgani et al. [51]) reported statistically significant decreased oncological outcomes in the group receiving (C)RT alone (regional control: 62–66% vs. 86%; isolated regional control: 80% vs. 95%; 3 year-OS: 42% vs. 66%; 3 year-DSS: 56% vs. 78%). Peters et al. [42] and Allal et al. [47] did not show differences between the groups and advocated for UFND only if patients were fit for surgery or needed to undergo general anesthesia for other reasons (e.g. dental extractions), emphasizing that care should be taken to reduce the time between surgery and RT as it may increase the risk of treatment failure [38,83]. In 11 out of the 15 studies which either directly reported or allowed the calculation of isolated regional control after UFND followed by (C)RT, the rates varied between 82% and 100% [31,37–42,45–47,50]. Isolated regional control rates in the literature reporting the results of (C)RT alone with and without post-(C)RT planned ND are between 87% and 100% [22–25,28,55,57,60–62,65,80,84–86] and 70% and 100% [16–18,28,71,73,74,87–90], respectively. Unfortunately, any direct comparison between these treatment strategies and oncological results is not possible. In contrast to the good results with planned ND, the outcome of isolated neck recurrences are poor and the efficacy of surgery is correlated with the stage of recurrence [32,91,92]. Mabanta et al. [32] reported the outcome of 51 patients with isolated neck persistence/recurrence after RT alone. Thirty-five percent of these cases had unresectable disease, and in those who underwent salvage ND, the 5-year regional control, DSS and OS after salvage was only 9%, 10% and 10%, respectively. More recently, the series of van der Putten et al. [91] described the outcome of 129 patients with regional residual or recurrent disease after initial CRT. Of these cases, 53% were considered inoperable. The 5-year regional control rate of the patients undergoing salvage ND was 79% and the OS 36%.

There is a growing body of evidence supporting the reliability of the clinical response assessment after CRT, and this has probably caused a shift of preference toward abandoning planned ND in cases of complete response. A critical appraisal of the literature provided here also gives some hints suggesting several potential advantages of UFND as a part of (C)RT organ-preservation protocols when compared to (C)RT alone.

Several limitations in our findings must be acknowledged. First, most study designs were retrospective. Second, some studies belong to an era prior to CRT, thus comparing UFND versus RT alone. Third, the study populations encompass a multitude of primary tumor sites and disease stages, with diagnostic and therapeutic procedures that are heterogeneous partly due to the large time span, but also due to different inter-institutional approaches. Additionally, current knowledge would impose to stratify patients according to Human Papilloma Virus status in order to obtain accurate interpretations in this subpopulation of patients. Finally, a meta-analysis could not be performed due to lack of randomized data, heterogeneity in outcome measures and reporting methodology. Despite these limitations, we believe that this first review about UFND provides clues supporting the evaluation of this strategy in a well-designed methodological basis.

Conclusions

Some of the few comparative studies suggest possible benefits of UFND approach in the (C)RT organ-preservation setting in terms of reduced acute toxicity and favorable oncological outcome, but the level of evidence remains low. Due to heterogeneity in study characteristics and reporting methodology, performing a meta-analysis is not reasonable. Well-designed randomized controlled trials analyzing benefits of outcome and cost-effectiveness are needed to further assess the efficacy of (C)RT with and without UFND.

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Conflict of interest statement

All authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2016.03.003.

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