



Surgery or Radiotherapy of the Primary Tumor in T1–2 Head and Neck Squamous Cell Carcinoma with Resectable N3 Nodes: A Multicenter GETTEC Study

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ABSTRACT

Background. The prognosis of advanced nodal (N3) squamous cell carcinoma of the head and neck (HNSCC) is poor. We investigated whether surgery or radiotherapy of early (T1–2) primary stage HSNCC is preferable to limit the overall morbidity after upfront neck dissection (uND) for N3 disease.

Methods. This retrospective multicentric Groupe d'Étude des Tumeurs de la Tête Et du Cou study included patients undergoing uND and surgery or radiotherapy of their primary. Prognostic factors were evaluated using propensity score matching to account for biases in performing surgery depending on primary site and stage.

Results. Of 189 T1–2, N3 HNSCC patients, 70 (37.0%) underwent uND: 42 with surgery of their primary and 28 with radiotherapy only. Radiotherapy alone was more frequent in patients with hypopharyngeal primaries. All local ($N = 3$) and regional ($N = 10$) relapses (included 2

locoregional relapses) occurred within the first 2 years. There were 16 distant metastatic failures. Five-year locoregional relapse and survival incidences were 15.7% and 66.5% and were similar regardless of the treatment of the primary. The overall morbidity rate was 65.2% and was similar after weighting by the inverse propensity score ($p = 0.148$). The only prognostic factor for morbidity was the radicality of the uND. Prolonged parenteral feeding was not more frequent in patients only irradiated to their primary ($p = 0.118$). Prolonged tracheostomy was more frequent after surgery of the primary.

Conclusions. In patients with T1–2, N3 HNSCC undergoing uND, radiotherapy and surgery of the primary yield similar oncological outcomes. Morbidity was related to the extent of neck dissection.

Chemoradiation therapy is recommended for some advanced (i.e., $\geq T3-4$, $N2-3$) head and neck squamous cell carcinoma (HNSCC). However, lymph nodes are more radioresistant than primaries,¹ and there is controversy regarding how best to manage the neck in case of advanced (i.e., $N2-3$) nodal disease.²⁻⁶ Several studies have investigated whether neck dissection should be performed upfront or following chemoradiation.^{7,8} A pivotal phase III

trial recently showed that neck dissection can be omitted by use of positron emission tomography (PET)-computed tomography (CT) in N2–3 HNSCC, thus providing an adequate (and more medicoeconomical) alternative to systematic upfront or postchemoradiation neck dissection.⁸ However, only a small proportion of the patients (< 9%) had N3 disease, and 75% had p16-positive oropharyngeal carcinoma. Consequently, no specific conclusion could be drawn regarding the optimal timing of neck dissection and multimodal management of bulky nodal disease of the neck in head and neck cancer related to tobacco and alcohol use. Moreover, N3 disease is often associated with advanced local disease, particularly in p16-negative patients. In such situations, chemoradiation is the standard treatment, and neck dissection is performed based on PET-CT guidance.

When N3 disease is associated with an early-stage (T1–2) primary, there is much less consensus regarding how the primary lesion should be managed. Due to bulky nodal disease, chemoradiation will eventually be performed on the neck. The primary may also be treated with definitive (chemo)radiation. A more conventional approach is surgical removal of the primary.

We investigated whether upfront surgery of the primary results in better locoregional control and increased morbidity with the addition of surgery of the primary in T1–2 HNSCC primaries with resected N3 nodal disease.

PATIENTS AND METHODS

This multicenter retrospective study included patients with resectable N3 nodes and T1–2 squamous cell carcinoma of the oropharynx, oral cavity, hypopharynx, or larynx. Exclusion criteria were history of cervical radiation therapy, initial metastatic disease, unknown primaries, or unresectable nodal disease, as neck dissection for bulky neck disease is itself morbid due to frequent immediate postoperative complications. Radiation therapy was by conformal [three-dimensional (3D)] or intensity-modulated radiation (IMRT) in association with cisplatin when not contraindicated. Patients operated for N3 disease received radiation of the neck and radiation or surgery of their primary. N3 disease was rated according to the 7th edition of the American Joint Committee on Cancer (AJCC)/International Union against Cancer (UICC) tumor–node–metastasis (TNM) classification criteria. Follow-up was according to the recommendations of the French Society of Otorhinolaryngology. Locoregional relapse was defined as persistence or recurrence of tumoral lymph node(s) or formation of a primary in the mucosa of the upper aerodigestive tract.

We collected patient, tumor, and treatment characteristics, as well as information regarding local, regional, and metastatic relapses by analysis of patient medical records from 11 French cancer centers between 2008 and 2016 as electronic report forms (<http://www.easy-crf.com>).

This institutional and GETTEC review board-approved protocol, validated in 2013, received authorization from the local ethics and Commission nationale de l'informatique et des libertés (CNIL) committees.

Statistics

Quantitative parameters are described as median, mean, and standard deviation, while qualitative parameters are described as frequency and percentage. Locoregional relapse was described with the Fine–Gray model, taking into account competing risks such as formation of metastases or death by any cause. The Kaplan–Meier method was used to describe overall survival (OS), defined as time between diagnosis and death, irrespective of cause. The prognostic value of surgery on primaries was studied using the bivariate Fine–Gray model, and the results are expressed as hazard ratio (HR) with 95% confidence interval (CI).

Due to potential selection biases (i.e., the choice of surgery on the primary could be according to patient characteristics), the results of these bivariate analyses were adjusted by the inverse probability of treatment weighting (IPTW) method.⁹ The propensity score was computed with either the presence or absence of surgery on the primary as dependent parameters, and with all of the described characteristics as independent parameters. The inverse probability of treatment, viz. surgery on the primary, was computed. The effect of surgery on the primary on locoregional relapse was estimated by the hazard ratio using a survival model weighted by the inverse probability of treatment (IPTW), as for the OS.

Morbidities were described according to surgery of the primary lesion and compared with Chi-square or Fisher's exact test. Weighting by the inverse probability of treatment was also performed for each morbidity using logistic regression. Prognostic factors of at least one morbidity were investigated using bivariate logistic regression. Parameters with p value < 0.1 were introduced in a multivariate logistic regression with backward selection.

All statistical analyses were carried out using SAS software (SAS Institute Inc., Cary, NC, USA). p values < 0.05 were considered statistically significant.

RESULTS

Out of 189 patients with T1–2, N3 disease, 70 (37.0%) had upfront neck dissection and none had induction chemotherapy. Management of the primary varied according to patient and tumor (Table 1). Patients with hypopharyngeal primaries were rarely operated on for their primary ($p = 0.002$), while patients with oral cavity primaries were more likely to undergo surgery of their primary ($p = 0.036$). Patients who had surgery of their primaries had lower doses for their primary site and neck.

Radical neck dissection sacrificing the jugular vein, XIth nerve, and sternocleidomastoid muscle was performed in 60.9% of patients. Four patients had to be reoperated due to complication, including three patients with surgery of their primary.

With median follow-up of 30.5 months (19–45 months), there were 1 local, 10 regional (including 2 locoregional), and 16 metastatic relapses. All locoregional relapses occurred within the first 24 months of follow-up. The incidence of locoregional relapse was 9.3% (95% CI 3.7–17.9%) at 12 months and 15.7% (95% CI 8.0–25.7%)

TABLE 1 Patient, tumor, and treatment characteristics

	All <i>N</i> = 70	No surgery of primary <i>N</i> = 28	Surgery of primary <i>N</i> = 42	<i>p</i> value
Sex (male), % (<i>n</i>)	90.0% (63)	96.4% (27)	85.7% (36)	0.230
Age, mean ± SD (years) > 60 years	61.2 ± 9.4 57.1% (40)	63.87 ± 10.0 67.9% (19)	59.4 ± 8.7 50.0% (21)	0.058 0.139
<i>T</i> stage, % (<i>n</i>)				0.435
<i>T</i> 1	48.6% (34)	42.9% (12)	52.4% (22)	
<i>T</i> 2	51.4% (36)	57.1% (16)	7.6% (20)	
Location of <i>T</i> , % (<i>n</i>)				
Oral cavity	10.3% (7)	0	17.1% (7)	0.036
Oropharynx	52.9% (36)	40.7% (11)	61.0% (25)	0.102
Hypopharynx	19.1% (13)	37.0% (10)	7.3% (3)	0.002
Larynx	20.6% (14)	22.2% (6)	19.5% (8)	0.787
Radical ND	60.9% (42)	33.3% (9)	42.9% (18)	0.429
Functional ND	39.1% (27)	59.3% (16)	43.9% (18)	
Location of node % (<i>n</i>)				
Level Ia/Ib	11.4% (8)	3.6% (1)	16.7% (7)	0.092
Level II/III	98.6% (69)	96.4% (27)	100.0% (42)	0.400
Level IV/V	50.0% (35)	53.6% (15)	47.6% (20)	0.626
Extracapsular spread	85.7% (60)	92.9% (26)	80.9% (34)	0.296
Sacrifices				
Jugular vein	55.7% (39)	63.0% (17)	52.4% (22)	0.387
Xth nerve	2.8% (2)	3.7% (1)	2.4% (1)	1
XIth nerve	38.6% (27)	44.4% (12)	35.7% (15)	0.468
XIIth nerve	6.9% (5)	18.5% (5)	0	0.007
Sternocleidomastoid muscle	47.1% (33)	59.3% (16)	40.5% (17)	0.127
Tumor emboli	40.0% (28)	50.0% (15)	33.3% (14)	0.163
Dose <i>T</i> , median [IQR]	70 [60–70]	70 [70–70]	66 [50–68]	< 0.001
Dose <i>T</i> ≥ 56 Gy, % (<i>n</i>)	79.1% (53)	100% (26)	65.8% (27)	0.008
Dose <i>T</i> ≥ 70 Gy, % (<i>n</i>)	46.3% (31)	84.6% (22)	21.9% (9)	< 0.001
Dose <i>N</i> , median [IQR]	66 [65–70]	70 [66–70]	66 [60–68]	0.018
Dose <i>N</i> ≥ 66 Gy, % (<i>n</i>)	73.1% (49)	80.8% (21)	68.3% (28)	0.262
Dose <i>N</i> ≥ 70 Gy, % (<i>n</i>)	35.8% (24)	53.8% (14)	24.4% (10)	0.014
Chemoradiation, % (<i>n</i>)	85.3% (58)	92.6% (25)	80.5% (33)	0.294

Bold values denote statistical significance

ND neck dissection, IQR interquartile range, SD standard deviation

at 60 months. Overall survival was 93.5% (95% CI 83.8–97.59%) at 12 months and 66.5% (95% CI 51.0–78.2%) at 60 months. Surgery of the primary tumor was not significantly associated with locoregional relapse (Fig. 1, HR = 0.56 [0.16–1.88], $p = 0.347$). After weighting by the inverse propensity score, the impact of surgery of the primary on locoregional relapse remained statistically insignificant (HR = 1.03 [0.35–3.00], $p = 0.956$). On bivariate analyses, none of the characteristics listed in Table 1 were significantly associated with locoregional relapse (data not shown). Overall survival was also not significantly different for the patients who underwent surgery of their primary (Fig. 2; HR = 0.80 [0.30–2.10], $p = 0.649$). These results were confirmed after weighting by the inverse propensity score (HR = 0.68 [0.25–1.88], $p = 0.462$).

Late morbidity occurred in over 65.2% of the entire patient cohort (Table 2). Morbidity was more frequent in patients without surgery of their primary (81.5% vs 54.8%, $p = 0.023$). Shoulder pain and Xth nerve palsies were equally frequent in both groups. XIIth nerve palsies were more frequent in patients undergoing radiotherapy only on their primary ($p = 0.008$). XIth nerve palsies were slightly more frequent but not statistically significantly so ($p = 0.068$). Although all patients underwent neck dissection, tracheostomy-related morbidity only occurred in patients who underwent surgery of their primaries. The use of a nasogastric feeding tube or gastrostomy 3 months after radiotherapy was more frequent for patients who underwent radiotherapy only of their primary ($p = 0.049$). After weighting by the inverse propensity score, there was not a significant difference (Table 2). Table 3 presents prognostic factors associated with the occurrence of at least one morbidity. On bivariate analyses, patients with oropharyngeal primaries had lower risk of morbidity (OR 0.33, 95% CI [0.11–0.95], $p = 0.039$) as did patients with functional versus radical neck dissection (OR 0.05, 95% CI

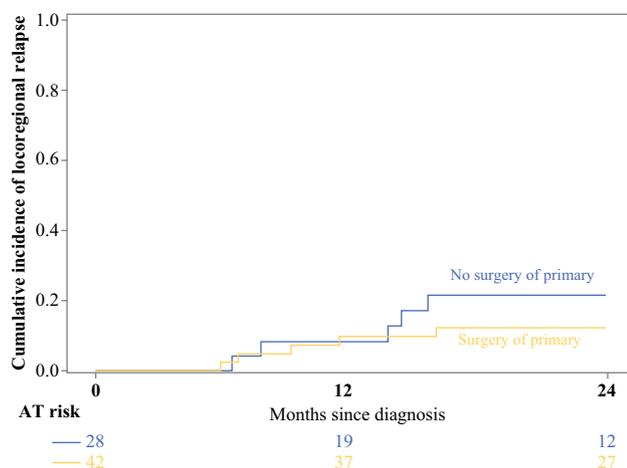


FIG. 1 Incidence of locoregional relapse

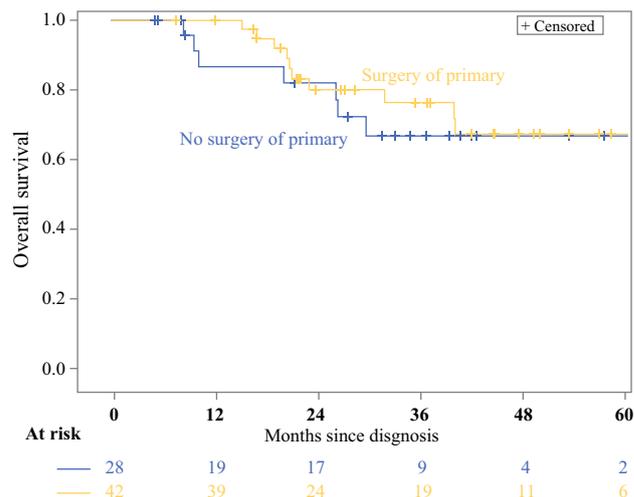


FIG. 2 Overall survival

[0.01–0.018], $p < 0.001$). In contrast, extranodal spread was a risk factor of morbidity (OR 5.76, 95% CI [1.33–24.95], $p = 0.019$). On multivariate analysis (Table 3), only functional neck dissection remained associated with lower risk of morbidity.

DISCUSSION

This study examined the relevance of the primary management modality in case of bulky nodal disease in terms of locoregional control, survival, and morbidity. With 70 patients (out of 189 N3 patients with stage T1 or T2 primary disease), this is the largest series published to date to address this specific question. Most N3 series or trials have included any T stage, with a focus on management of the neck.^{7,10–22} An exception is the publication by Smyth et al., which included 43 patients with T1–2 N3 disease.²³ Others have addressed the T1–2 issue with less homogenous nodal stage selection.^{24–26}

Our patient selection inherently relied on resectable nodal disease (among N3 disease patients), for which the relevance of reducing morbidity is particularly critical. The 5-year locoregional relapse and survival rates were much better than for unselected N3 populations, and are similar to those reported by Smyth et al.²² Only 70/189 patients (37%) initially had a neck dissection. As this study was conducted before the large PETNECK study that found equivalent oncological results with planned or response-based neck dissection, French centers are more likely to perform upfront neck dissection with N3 disease.²⁷

We found that the oncological outcomes were similar for patients undergoing surgery of their primary or (chemo)radiation only. As is often the case, patients undergoing surgery had more favorable initial patient and tumor characteristics. Unfortunately, the tumor

TABLE 2 Morbidity rates by management of the primary

	All N = 70	No surgery of primary N = 28	Surgery of primary N = 42	p value	Weighted p value*
At least one morbidity	65.2% (45)	81.5% (22)	54.8% (23)	0.023	0.148
Palsy X	4.3% (3)	3.7% (1)	4.8% (2)	1	0.885
Palsy XI	42.0% (29)	55.6% (15)	33.3% (14)	0.068	0.467
Palsy XII	7.3% (5)	18.5% (5)	0	0.008	nc
Painful shoulder	37.3% (25)	37.0% (10)	37.5% (15)	1	0.739
Tracheostomy	7.2% (5)	0	11.9% (5)	0.146	nc
Feeding tube or gastrostomy 3 months after the end of the radiotherapy	17.4% (12)	29.6% (8)	9.5% (4)	0.049	0.118

Bold values denote statistical significance

nc not computed due to no event in one stratum

*p value after weighting by inverse propensity score

TABLE 3 Prognostic factors of morbidity

	Bivariate		Multivariate	
	OR [95% CI]	p value	OR [95% CI]	p value
Sex (male vs female)	1.46 [0.30–7.16]	0.638		
Age > 60 years	1.50 [0.55–4.07]	0.426		
T2 versus T1	0.486 [0.17–1.32]	0.156		
Tumor location				
Oral cavity	0.71 [0.15–3.51]	0.683		
Oropharynx	0.33 [0.11–0.95]	0.039		
Hypopharynx	1.85 [0.45–7.63]	0.393		
Larynx	4.26 [0.86–20.95]	0.075		
ND functional versus radical	0.05 [0.01–0.018]	< 0.001	0.05 [0.01–0.018]	< 0.001
Extracapsular spread	5.76 [1.33–24.95]	0.019		
Tumor emboli	2.62 [0.88–7.84]	0.084		
Node location				
Level Ia/Ib	0.49 [0.11–2.15]	0.343		
Level II/III	nc**	–		
Level III/IV	2.74 [0.97–7.70]	0.056		
Surgery of T	0.25 [0.09–0.86]	0.027		
Dose T ≥ 56 Gy	2.11 [0.64–7.00]	0.219		
Dose N ≥ 66 Gy	1.20 [0.39–3.65]	0.751		
Chemoradiation	2.05 [0.53–7.96]	0.298		

ND neck dissection, OR odds ratio, NC not computed

**Only one patient in level Ia/Ib

characteristics such as the hypopharyngeal site, which was rarely operated on, are often associated with worse locoregional control than oropharyngeal HNSCC.²⁸

The overall morbidity rate, which included morbidity from the neck dissection, postoperative nodal chemoradiation, and management of the primary, was comparable to that reported by Al-Mamgami et al.²⁹ Lower acute pain and mucositis rates have, however, been reported.³⁰ These

studies included N3 disease with T1–4 primary disease and did not allow for accurate analysis of treatment-induced morbidity in early-stage primaries.

We showed that the XIth and XIIth nerve palsy rates tended to be higher in irradiated patients but became similar after accounting for primary site and stage by propensity score weighting. Of note, the dose to the primary lesion was higher in the irradiated group, as it was the sole treatment. A higher dose was also delivered to the

nodes (70 vs 66 Gy, which is the standard dose postoperatively for N3 disease unless there is gross residual disease). This difference in dose may reflect a number of unfavorable nodal characteristics that are not fully captured by the nodal item of the TNM classification (e.g., presence of gross residual disease and extensive extracapsular spread). Thus, an increase in XIth nerve morbidity with (chemo)radiation in a small patient population and with borderline significance should be interpreted with a degree of caution, especially since this result was not significant after weighting by the inverse propensity score.

Similarly, we observed less use of feeding tubes or gastrostomy 3 months after radiation therapy in the group that had undergone surgery of their primary. This may be explained by a significant reduction of the median dose with surgical treatment of the primary lesion (70 Gy without surgery of the primary versus 66 Gy with surgery; 84.6% had a dose \geq 70 Gy without surgery of the primary versus 21.9% with surgery). It could also indicate that a nonsurgical treatment was chosen for hypopharyngeal primaries due to the high rate of surgical morbidity for this tumor site. Machtay et al.^{31,32} also found that a high dose to the hypopharynx was associated with a high rate of morbidity and feeding tube-related morbidity with nonoperated primaries. Finally, surgery of oropharyngeal primaries seems a reasonable option, although whether this is also the case for hypopharyngeal primaries remains to be determined. Doubt is also cast on whether the dose can be reduced with small oropharyngeal primaries and that radiotherapy of the primary might not be as morbid.

Intriguingly, palsy of the XIIth cranial nerves was higher with (chemo)radiation, but palsies occurred after neck dissection and before radiotherapy. Tracheostomy-related morbidity only occurred with surgical (*T*) patients.

Finally, morbidity was higher in patients who had radiotherapy only of their primary, although the only prognostic factor was the extent of the neck dissection, with worse morbidity after radical neck dissection. This suggests that patients undergoing RT only of their primary had additional worse factors than *T* and primary site that are again not fully captured by the nodal item of the TNM classification. The technique of radiotherapy (IMRT, 3DCRT) was not collected in our database. Cumulative morbidity has been observed after multimodality treatments.³² In light of the PETNECK trial and its favorable morbidity data, it might be appropriate to avoid upfront neck dissection in these patients and to deliver primary chemoradiation to both the primary lesion and the nodes.^{7, 8} However, the percentage of patients who may no longer require neck dissection and instead exclusively receive nonsurgical treatment of their primary needs to be determined in case of N3 disease in real life.

One of the limitations of this study is the N3 staging using the 7th edition of the AJCC/UICC TNM classification criteria. In particular, there were 36 oropharyngeal cancer patients, and the p16 status was only available in 11 cases. It is unlikely, however, that the p16 cases amounted to a significant percentage, and HNSCC patients in France are predominantly heavy smokers.³³ Thus, we believe that downstaging would not be relevant from this series. Another limitation is that oropharyngeal primaries were more likely to be operated on. Oropharyngeal carcinomas, especially those with human papillomavirus (HPV) as the causal factor, have an excellent radiation response profile, while hypopharyngeal carcinomas are often hypoxic and more likely to be radioresistant. However, this is more relevant to geographic areas with a predominance of HPV-positive oropharyngeal carcinomas in nonsmokers. Another bias is that morbidity of surgery of the primary lesion and the nodes with hypopharyngeal primaries is an important consideration that can greatly influence treatment choices that favor surgery.²⁸ Moreover, as this study is retrospective, patients who had radiotherapy on their primary could have had more extended nodal presentation, as the identification of the radicality of the neck dissection was the only prognostic factor of morbidity on multivariate analysis. This finding suggests that radiotherapy had a worse nodal presentation that cannot be captured with the 7th and 8th TNM classification. Finally, the selection to assess morbidity of the surgery of the primary lesion led us to exclude patients who did not undergo neck dissection. Residual biases cannot be excluded. The sample size might not be large enough to address the bias caused by the location of *T*, although propensity score matching was used. Larger prospective cohort studies with morbidity scoring at baseline and during follow-up are necessary to investigate morbidity and quality of life in this setting.

CONCLUSIONS

In patients with T1–2, N3 HNSCC undergoing upfront neck dissection, chemoradiation and surgery of the primary tumor resulted in similar oncological outcomes. Morbidity was related to the extent of neck dissection, suggesting that the TNM classification cannot properly address node-related prognostication of morbidity. Prospective studies with toxicity (such as dysphagia) and quality-of-life analyses remain necessary to better investigate morbidity and its consequences by primary site.

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