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HEAD AND NECK

N3 (> 6 cm) squamous cell carcinoma of the head and neck: outcomes and predictive factors in 104 patients

Il carcinoma squamocellulare della testa e collo con N3 (> 6 cm): risultati e fattori prognostici in 104 pazienti

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SUMMARY

Objective. To report outcome and predictive factors in patients with N3 (> 6 cm) non-metastatic locally advanced head and neck squamous cell carcinoma (LAHNSCC) treated with a conservative approach or with initial surgery.

Methods. 104 patients were included: 69 treated with radiotherapy (RT) ± chemotherapy (CT) and 35 with nodal surgery with or without primary tumour resection, which was completed in 30 patients by adjuvant RT ± CT. Positron-emission tomography-computed tomography (PET-CT) guided surveillance after RT ± CT was standard.

Results. Two-year overall survival (OS) and locoregional control (LRC) were 39.4% and 37.5%, respectively. In univariate analysis, body mass index (BMI), performance status (PS), p16 status and haemoglobin value influenced OS and disease-free survival (DFS). In multivariate analysis, p16 positive status and BMI ≥ 25 remained independent prognostic factors for better OS (p = 0.023) and DFS (p = 0.002). Only under/normal weight remained an independent and adverse significant prognostic factor in multivariate analysis for regional control (RC). Patients treated with primary RT ± CT had slightly better 2-year OS (43.5% *versus* 33.3%, p = 0.31).

Conclusions. Patients with N3 LAHNSCC have poor prognosis, but long term LRC is achievable, especially in overweight patients and those with a good PS.

KEY WORDS: N3 (> 6 cm), head and neck cancer, surgery, radiotherapy, prognostic factors

RIASSUNTO

***Obiettivo**. Analizzare i risultati e fattori predittivi in pazienti con carcinoma a cellule squamose della testa e del collo localmente avanzato non metastatico con N3 (> 6 cm) (LAHNSCC N3) trattati con un approccio conservativo o con intervento chirurgico*

***Metodi**. Sono stati inclusi 104 pazienti: 69 trattati con radioterapia (RT) ± chemioterapia (CT) e 35 con chirurgia linfonodale con o senza resezione del tumore primario, di cui 30 pazienti con RT ± CT adiuvante. La sorveglianza dopo RT ± CT è stata eseguita mediante tomografia computerizzata a emissione di positroni (PET-TC)*

***Risultati**. La sopravvivenza globale (OS) a 2 anni e il controllo locoregionale (LRC) erano rispettivamente del 39,4% e del 37,5%. Nell'analisi univariata, l'indice di massa corporea (BMI), il performance status (PS), lo stato di p16 e il valore dell'emoglobina hanno influenzato l'OS e la sopravvivenza libera da malattia (DFS). Nell'analisi multivariata, la positività di p16 e il BMI ≥ 25 sono rimasti fattori prognostici indipendenti per una migliore OS (p = 0,023) e DFS (p = 0,002). Lo stato di malnutrizione o normale status nutrizionale sono rimasti fattori prognostici significativi indipendenti e negativi nell'analisi multivariata per il controllo regionale (RC). I pazienti trattati con RT ± CT primaria avevano una OS a 2 anni leggermente migliore (43,5% contro 33,3%, p = 0,31).*

***Conclusioni**. I pazienti con LAHNSCC N3 hanno una prognosi sfavorevole, ma è possibile ottenere un LRC a lungo termine, specialmente nei pazienti in sovrappeso e in quelli con un buon PS.*

PAROLE CHIAVE: *N > 6 cm, tumore della testa e del collo, chirurgia, radioterapia, fattori prognostici*

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Introduction

Two-thirds of patients diagnosed with head and neck squamous cell carcinoma (HNSCC) present with locally advanced stage III-IV disease at diagnosis. Among these, patients with metastatic lymph nodes measuring > 6 cm have a poor prognosis with a 2-year disease-free survival (DFS) of approximately 30%, especially because of a high rate of distant metastases [1]. Although it is generally appreciated that the prognosis of such patients is poor, aggressive treatment improves survival and should be considered even in patients with high tumour burden. However, the optimal treatment strategy for large neck disease remains a controversial issue [2]. Chemoradiotherapy (CRT) has now been established as one of the standard of care for unresectable locally-advanced HNSCC (LAHNSCC) in multiple randomised trials [3], but outcome of patients with N3 (> 6 cm) are poorly defined as these patients represent only 10% of patients with LAHNSCC and are routinely combined with patients with smaller nodes (N1-2) in clinical trials.

In this study, we aimed to report outcomes of patients with N3 LAHNSCC treated with definitive radiotherapy (RT) and with upfront surgery to find prognostic factors in this population.

Materials and methods

Patient population

All patients with histologically N3 LAHNSCC according to the 7th American Joint Committee on Cancer (AJCC) and treated with curative intent between 2005 and 2016 were retrospectively identified at our two institutions. As the TNM classification was updated in December 2016, surgical patients were restaged following the 8th version: in case of extracapsular extension, patients were classified as pN3b, while the others were classified pN3a. Patients with nasopharyngeal or salivary gland cancer were not considered. The need for informed consent was waived by the medical ethics of our institution because of the retrospective nature of the study at the time it was designed.

Treatment characteristics

Treatment decisions were made at the weekly multidisciplinary team meeting. Of note, p16 status was not routinely performed at the time patients were treated and was retrospectively analysed for oropharyngeal tumours for the purpose of this study. As such, the fact that some tumours were human papillomavirus (HPV)-driven did not influence the therapeutic management.

- Surgery
  Surgery consisted of a unilateral or bilateral neck dissection with or without a resection of the primary tumour.
- Chemotherapy
  Induction CT (ICT) was considered in patients with good performance status (ECOG: 0-1). Standard ICT consisted of 2-3 cycles of PF (cisplatin (CDDP) and 5-fluorouracil (5FU) 800 mg/m^2 every 3 weeks) or from 2011 TPF (docetaxel 75 mg/m^2, CDDP 75 mg/m^2 and 5FU, 750 mg/m^2 every 3 weeks) in selective fit patients. Regarding concomitant CT, CDDP delivered every three weeks (100 mg/m^2) was the standard regimen from 2011. In case of contraindications to CDDP, weekly carboplatin (area under curve 2) or cetuximab were substituted. Before 2011, patients received either a FP regimen consisted of 5-FU and CDDP at a 3 week interval.
- Radiotherapy
  The standard biologically equivalent dose in 2 Grays (Gy) fractions to the primary tumour and involved nodes was typically 70 Gy. Prophylactic dose to uninvolved nodes was 56 Gy in 28 fractions, although dose regimens could slightly vary at the clinician's discretion. Postoperative delivered dose was 66 Gy in case of extracapsular extension or positive margins. Patients were irradiated using a three-dimensional (3D) conformal RT or, from 2014, Intensity Modulated Radiotherapy (IMRT).

Response assessment and follow-up

To assess therapeutic response, computed tomography (CT) was performed 3 months after treatment completion until 2008, when these imaging modalities were substituted with 18-flurodeoxyglucose (^{18}FDG) positron emission tomography (PET)-CT. Tumour response was accordingly assessed based on the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST) or the Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) [4].

Salvage neck dissection was considered after RT only in the case of incomplete nodal response alongside with complete response (CR) at the primary site.

Clinical follow-up consisted of physical examination every second month until 2 years after diagnosis, every four months during the third year, and every six months up to 5 years.

Statistical analysis

Isolated neck failure was defined as recurrence in the neck after completion of treatment (i.e., including neck dissection if done) or as unresectable persistent neck disease after treatment, with primary and distant disease control.

Chi-square and Fisher's exact tests were used to compare variables between groups. Survival curves were plotted

based on the Kaplan-Meier method, and compared using the log-rank test. Impact of clinical variables (gender, age, body mass index (BMI), performance status (PS), smoking habit, haemoglobin value (Hb), primary site, T stage, presence of extracapsular extension according to the 8th AJCC version for patients treated with surgery, p16 status and primary treatment modality (RT versus surgery) on overall survival (OS), regional control (RC), locoregional control (LRC) and DFS was analysed by univariate (UVA) and multivariate analysis (MVA). Statistical significance was defined as a p value of < 0.05. A subgroup analysis on patients with oropharyngeal tumours was also performed.

Results

Patient and tumour characteristics

One hundred and four patients with N3 (> 6 cm) LAHNSCC were indentified and included in the analysis. The majority of patients were male (93.3%) and had oropharyngeal (38.5%) or hypopharyngeal (40.4%) cancer. Median age was 61.7 years (range, 40.4-85.9). There were no significant differences in baseline characteristics between patients treated with definitive radio(chemo)therapy and those treated with initial surgery, except for tumour size which was larger in patients who underwent RT ($p =< 0.001$; Tab. I). Median maximal lymph node diameter was 6.7 cm (range 6-15).

Treatment characteristics

Two main groups of patients were identified: group 1 included patients who were not suitable for surgery (poor performance status, nodes or primary tumour unresectable) and were treated with concomitant CRT (n = 28, 40.6%), RT alone (n = 11, 15.9%), ICT followed by CRT (n = 23, 33.4%), or ICT followed by RT alone (n = 7, 10.1%). Patients in group 2 were treated by surgery, including surgery alone (n = 5, 14.3%) because of adjuvant treatment refusal (n = 1), dramatically rapid tumour progression (n = 1), postoperative complications (n = 2) or both (n = 1), surgery followed by CRT (n = 15, 42.9%) or RT alone (n = 11, 31.4%), and surgery preceded by ICT and followed by post-operative CRT (n = 4, 11.4%; Tab. II).

Treatment response

At the first evaluation 3 months after treatment completion, all but 2 patients could be analysed for therapeutic response. Among these, 43 had a PET and 59 had a CT to assess therapeutic response. Thirty-two patients (46.4%) and 26 (34.8%) patients in group 1 and 14 (38.9%) and 14 (38.9%) patients in group 2 achieved a CR in the primary

Table I. Patients and tumour characteristics.

Characteristics	Radiotherapy group		Surgery group	
	n = 69	%	n = 35	%
Age: years and (range)	62.1 (46.9-85.9)		63 (40.4-81.3)	
Sex				
Male	65	94.2	32	91.4
Female	4	5.8	3	8.6
PS				
0-1	41	59.4	17	48.6
2	28	40.6	18	51.4
Smoking				
Nonsmoker	3	4.4	0	0.0
Ex-smoker	21	30.4	11	31.4
Current smoker	45	65.2	24	68.6
BMI before treatment				
< 18.5	7	10.1	2	5.7
18.5 -< 25	26	37.7	15	42.9
25 -< 30	22	31.9	5	14.3
≥ 30	6	8.7	2	5.7
NA	8	11.6	11	31.4
Hb before CRT				
≥ 13.5 (M) or 12.5 (F)	20	28.9	7	20
< 13.5 or 12.5	32	46.4	9	25.7
NA	17	24.7	19	54.3
Primary tumour site				
CUP	6	8.7	7	20
Oral cavity	5	7.2	3	8.6
Oropharynx	28	40.6	11	31.4
Hypopharynx	24	34.8	10	28.6
Larynx	1	1.4	1	2.9
2 Sites	5	7.2	3	8.6
T stage				
T1-T2	11	15.9	16	45.7
T3-T4	52	75.4	12	34.3
Tx (CUP)	6	8.7	7	20
pN3 stage for group 2 (n = 35)				
pN3a	-	-	4	11.4
pN3b	-	-	31	88.6
p16 status for OPC (n = 40)	n = 29		n = 11	
Positive	8	27.6	2	18.2
Negative	16	55.2	9	81.8
NA	5	17.2	0	0

PS: performance status; BMI: body-mass index; Hb: haemoglobin; CRT: chemoradiotherapy; M: male; F: female; NA: not available; CUP: cancer of unknown primary origin; OPC: oropharynx; HPC: hypopharynx; HPV: human papillomavirus.

and nodal sites, respectively. Among the 40 patients who achieved a nodal CR, 7 relapsed regionally during follow-up. Thirty-eight patients (36.5%) (25 in group 1 and 13 in group 2) achieved a CR at the primary site and the neck [including 8 carcinoma of unknown primary (CUP)], 21 (20.2%) achieved CR at the primary site only (including 5 CUP) and 35 (33.7%) did not achieve CR at either the primary site or in the neck.

Among the 21 patients who did achieve CR at the primary site but not in the neck, 5 were diagnosed with metastatic disease and therefore did not proceed to neck dissection, 8 patients were not eligible to neck dissection as the mass was deemed unresectable, and 8 had a neck dissection which showed proliferating cancer cells.

Overall survival and disease-free survival

Median follow-up of surviving patients was 49.0 months (range, 23.2-133.9). At last follow-up, 69 (66.3%) patients had died of HNSCC, 5 following treatment complications (4.8%), 10 (9.6%) of an unrelated cause (including 5 for other cancers), 4 (3.8%) were alive with disease and 16 (15.4%) were alive and free of disease.

The 2- and 5-year OS rates were 39.4% and 20.0%, respectively, while the median OS was 16.0 months (95% CI, 10.4-21.6). The 2- and 5-year DFS rates were 29.0% and 18.3% respectively, and the median DFS was 6.2 months (95% CI, 4.2-8.1).

Patients treated with primary RT ± CT had slightly better OS than those treated with primary surgery with a 5-year OS of 23.2% (95% CI 12.4-34.0) *vs* 13.0% (IC95%, 0.8-26.8) and a median survival of 18.2 months (IC95 9.7-26.7) *vs* 14.9 months (95% CI, 9.0-20.9), but this difference was not statistically significant (p = 0.308).

Locoregional and distant control

At last follow up, 74 of all patients (71.2%) exhibited treatment failure: 61 patients (58.7%) experienced neck failure, 56 (53.8%) primary site failure and 37 (35.6%) distant metastasis. Only 4 patients (3.8%) had isolated neck failure (Tab. III). In summary, 82.4%, 75.7% and 50.0% of all cases of failures involved regional relapse, local relapse and distant metastasis, respectively. The 2- and 5-year LRC rates were 37.5% (95% CI, 27.7-47.3) and 29.8% (95% CI, 19.2-40.4), respectively.

Neither RC nor LRC were influenced by the therapeutic modality (p = 0.963 and 0.857 respectively).

Prognostics factors

On UVA, BMI ≥ 25, PS 0-1, positive p16 status and Hb values ≥ 13.5 for men and ≥ 12.5 for women were found to significantly influence OS, with a median survival of 89.7 months (95% CI, 0.0-182.9) versus 9.9 months (95% CI, 7.8-12.0) in favour of patients with p16 positive oropharyngeal cancer. On MVA, p16 positive status remained independently correlated with better OS (*p = 0.023*; Fig. 1; Tab. IV).

Regarding DFS, the same prognostic factors for better survival were found, while only overweight/obesity remained an independent prognostic factor in MVA (*p = 0.002*).

The UVA for RC showed that BMI ≥ 25, PS 0-1 and haemoglobin values were statistically significant, while being overweight (p = 0.001) and having a good general state (*p = 0.009*) remained independent prognostic factors in MVA, with a 5-years RC of 59.5% (95% CI, 42.7-76.3) for overweight/obese patients vs 28.6% (95% CI, 15.0-42.2) for normal/underweight patients (Fig. 2).

Table II. Treatment characteristics.

Treatment	Radiotherapy group		Surgery group	
	n = 69	%	n = 35	%
Induction chemotherapy				
Yes	30	43.5	4	11.4
FP	5	16.7	3	75.0
TPF	24	80.0	1	25.0
Carboplatin-cetuximab	1	3.3	0	0
None	39	56.5	31	88.6
Concomitant chemotherapy				
Yes	51	73.9	19	54.3
CDDP	26	37.7	10	28.6
Cetuximab	15	21.7	3	8.6
FP	8	11.6	5	14.3
Carboplatin	2	2.9	1	2.9
None	18	26.1	16	45.7
Radiotherapy				
Yes/dose (Gy)/Fr	66	95.7	30	85.7
30/10 + 25/10	2	3.0	0	0
60-66/30-33	0	0	18	60.0
70/35	62	93.9	10	33.3
Early stopping*	2	3.1	2	6.7
None	0	0	5	14.3
Planned but not made*	3	4.3	-	-
Radiation technique (n = 96)	n = 66		n = 30	
VMAT	8	12.1	0	0
IMRT	26	39.4	11	31.4
3D	32	48.5	19	54.3

FP : 5-fluorouracil (800mg/m² days 2-5) + cisplatin (80 mg/m² day 1); TPF: docetaxel (75 mg/m² day 1), cisplatin (75 mg/m² day 1) and 5FU (750 mg/m² days 2-5); CDDP: cisplatin; Cet: cetuximab; Gy: Grays; Fr: fractions; VMAT: volumetric modulated arc therapy; IMRT: intensity modulated radiotherapy; 3D: three dimensional radiotherapy
**: due to worsening of the general state and/or obvious progression.*

Table III. Status at last follow up.

Status at last follow-up	Radiotherapy group	Surgery group	All
Progression / Site of failure	49 (71.0%)	25 (71.4%)	74 (71.7%)
Isolated primary	1	0	1
Isolated nodal	3*	1	4
Primary and nodal	20#	6	26
Primary and nodal (without distant reassessment)	3	3	6
Primary nodal and distant	13 *	4	17
Primary and distant	3*	3	6
Nodal and distant	4	4	8
Isolated distant	2	4*	6
Without failure	20 (29%)	10 (28.6%)	30 (28.3%)
Remission	12	4	16
After completion of initial treatment	10	4	14
After salvage ND	2	0	2
Death due to treatment's complications	2	3	5
Death – other reasons	6	3	9

**: one still alive with disease; #: one died of pulmonary cancer*
ND: neck dissection.

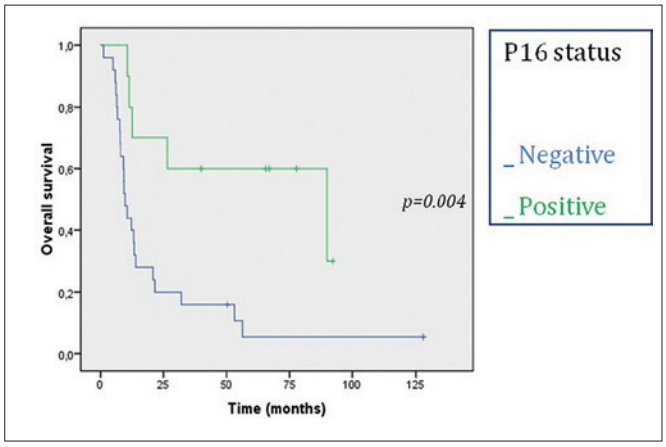

Figure 1. Kaplan-Meier curve for overall survival based on p16 expression.

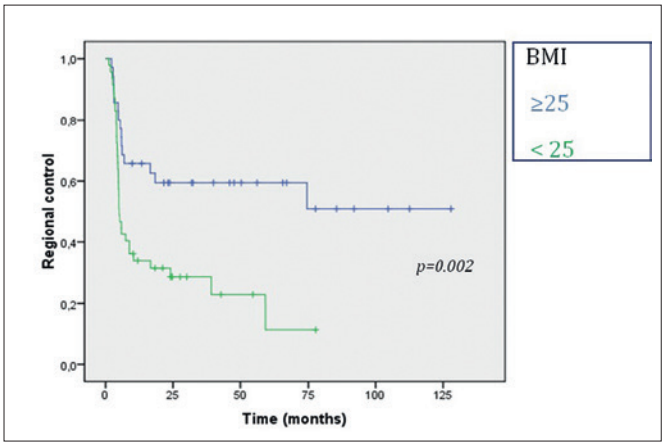

Figure 2. Kaplan-Meier curve for regional control based on body mass index.

LRC was significantly better in overweight/obese patients, in patients with PS 0-1, in those having haemoglobin values ≥ 13.5-12.5g/dl and in case of p16 positive status, but only BMI ≥ 25 remained an independent prognostic factor (55.0% *vs* 15.3% at 5-year (*p = 0.002*); supplementary Tab. I).

We also studied prognostic factors in patients treated with definitive RT. Age ≥ 62 years, BMI ≥ 25, PS 0-1, haemoglobin value and p16 positive status conferred significantly better OS. On MVA, age, PS and p16 status remained independent prognostic factors for survival. Regarding LRC, only BMI ≥ 25 remained an independent factor on MVA. Neither OS nor LRC was influenced by the administration of ICT (*p =0.339* and *p = 0.837*, respectively).

In the subgroup analysis, among patients diagnosed with oropharyngeal cancer, we found a significant difference for patients with p16 positive tumours in terms of OS for group 1 (62.5% *vs* 6.3% at 5 years, p = 0.011) whereas this survival advantage was not found for patients treated with primary surgery (*p = 0.363*).

Discussion

We found a relatively poor 5-year OS of 20% in this large

Table IV. Uni- and multivariate analysis for overall survival.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% IC	*p*	HR	95% IC	*p*
Patients parameters						
Sex (male *versus* female)	0.70	(0.26-1.92)	0.494			
Age (> 62 *vs* ≤ 62)	1.36	(0.88-2.11)	0.162			
BMI (< 25 *vs* ≥ 25)	2.45	(1.43-4.18)	**0.001**	1.36	(0.30-6.15)	0.686
PS (≥ 2 *vs* 0-1)	3.82	(2.36-6.18)	**< 0.001**	2.48	(0.85-7.25)	0.095
Smoking (active vs none or past)	1.33	(0.84-2.12)	0.226			
Hb (< 13.5 or 12.5)	2.21	(1.23-3.98)	**0.008**	0.79	(0.22 2.78)	0.714
Tumour parameters						
Site (others *vs* oropharynx)	0.97	(0.62-1.52)	0.911			
T stage (T3-4 *vs* T1-2)	1.22	(0.77-1.92)	0.397			
N stage (pN3b *vs* pN3a)	1.95	(0.46-8.31)	0.366			
p16 status (+ *vs* -)	0.26	(0.09-0.70)	**0.008**	0.17	(0.04-0.78)	**0.023**
Treatment						
Surgery *vs* radiotherapy	1.22	(0.78-1.92)	0.383			

Hb: haemoglobin; BMI: body-mass index; PS: performance status.

cohort of patients treated for HNSCC with N3 (> 6 cm). This is consistent with previous series reporting on outcomes after CRT [2,5,6] and surgery [7]. Primary surgery does not seem to influence outcomes compared to RT ± CT. As such, radiation-based conservative treatment with PET-guided surveillance does seem appropriate even in very advanced regional disease.

This is in agreement with a retrospective series of 69 patients with N3 (> 6 cm) treated with definitive RT ± CT (n = 42) or surgery (n = 27), without any significant difference in 3–year OS (48% *vs* 41%, respectively) [2].

Because nodes > 6 cm were deemed to be unlikely eradicated by non-surgical means alone, neck dissection after RT was historically recommended in patients with N2-N3 disease. More recently, the integration of PET-CT has improved the accuracy of response assessment in the setting of residual nodal disease thanks to its high negative predictive value [8]. On the basis of data from the recent British phase III PET-NECK trial, the strategy of systematic planned neck dissection after RT is no longer justified in patients who achieve a CR on PET-CT at 3 months following RT completion [9]. However, N3 (> 6 cm) patients represented only 17 of the 564 patients included in this trial, making it difficult to draw any conclusion on this subgroup of patients.

In our study, the rate of isolated neck failure (3.8%) was low. These results suggest the high negative predictive value of PET still seems to be maintained with nodes > 6 cm and that planned neck dissection is unnecessary even in patients with large nodes > 6 cm if they achieve metabolic CR. This is in agreement with other studies [8,10].

The majority of failures were locoregional in our cohort, and the rate of distant metastasis (35.6%) was the same to that found in other series [1,2,5,10-12]. Indeed, these patients are at high risk of having clinically occult micrometastatic disease on presentation and this raises the question on the benefit of ICT to reduce the rate of distant metastasis. We did not find any benefit of ICT and this is in line with recent randomised trials which failed to show a survival benefit of ICT in combination with CRT [13-15]. The recent phase III trial of the French GORTEC group which tested the benefit of induction TPF chemotherapy followed by RT associated with cetuximab over CRT specifically in N2b-N3 patients suggests that the rate of distant metastases is decreased by the use of ICT, but without improvement in OS (*p = 0.48*) [16].

Many other therapeutic strategies are currently being tested with the aim to improve outcomes in patients with LAHN-SCC, such as RT dose escalation, gemcitabine-based chemoradiation [17], altered fractionation with hypoxic cells radiosensitiser (NCT01880359) and, more recently, immunotherapy in combination with RT. Indeed, immune checkpoint inhibitors have become a standard in the treatment of recurrent or metastatic HNSCC and are now being tested prospectively in the locally-advanced setting. Through immunogenic cancer cell death and effect on the tumour microenvironment and vasculature, RT may enhance the effect of immune checkpoints inhibitors [18].

The role of PS is widely known to predict response to treatment and survival [19]. More surprising is the positive impact of BMI ≥ 25 kg/m^2 on outcomes. Historically, studies

have demonstrated that patients with low BMI have worse outcome [20], an expected finding given the poor nutritional status of underweight patients. However, those studies did not address whether overweight patients have better survival rates than normal weight patients. We found that being overweight (BMI ≥ 25) at diagnosis conferred a significantly better prognosis with a 5-years LRC of 55% versus 15% in favour of overweight patients.

This observation has already been reported in a study of 578 patients with HNSCC, showing that higher BMI was associated with drastically better survival ($p < 0.001$) with 5-year OS rates ranging from 33.8% in underweight to 74.8% and 76.0% in overweight and obese patients, respectively. This study also showed that overweight and obese patients had equivalent survival, and these two groups were then combined in subsequent analyses [21].

The relationship between poor survival and normal/underweight may represent underlying patient's comorbidity, frailty, or poor baseline nutritional health. However, BMI may not be the right measure to assess body composition, as the worse prognosis seems to be seen in patients with sarcopenic obesity [22].

HPV status has now been established as a reliable prognostic biomarker for oropharyngeal cancer [23]. We found that patients with HPV/p16 positive oropharyngeal cancer had better prognosis compared to patients with HPV/p16 negative tumours, with a 5-year OS of 62.5% *vs* 6.3% ($p = 0.004$). HPV positive oropharynx cancer had a significantly better OS ($p = 0.011$) in the RT group, specifically reflecting the higher radiosensitivity of this disease subtype [24]. This contributes to the notion that HPV-positive and HPV-negative HNSCC are two distinct diseases, which may require individual treatment optimisation.

We acknowledge that this study has the limitation of its retrospective design and therefore inherent bias. A major limitation is the heterogeneity of treatment modalities and post-treatment assessments, over a long period of time during which several specialists with possibly different levels of expertise were involved. Moreover, assessment of N3 (> 6 cm) disease was sometimes difficult in case of continuity between nodes and primary tumours. This work was also performed before the revision of the TNM classification. In case of surgery, CUPs are now classified as HPV-related oropharynx cancer in case of p16 positivity, or as nasopharyngeal tumours in case of presence of Epstein-Barr virus. The two patients with resected HPV-related oropharyngeal cancer in our study would now be classified as pN2 disease, reflecting the better prognosis of these patients. Finally, although not statistically different, the two groups were not perfectly balanced in terms of tumour locations: more patients with CUP and fewer with oropharyngeal tumours were treated with initial surgery, and p16 positive tumours were also more represented in the RT group, and this may have influenced outcomes.

Conclusions

Patients with N3 (> 6 cm) LAHNSCC have poor prognosis, but long term LRC is achievable, especially in those with a good performance status and BMI ≥ 25, and long term survival is possible for patients with HPV-related oropharyngeal cancer.

References

1 Adams G, Porceddu SV, Pryor DI, et al. Outcomes after primary chemoradiotherapy for N3 (> 6 cm) head and neck squamous cell carcinoma after an FDG-PET - guided neck management policy. Head Neck 2014;36:1200-1206. https://doi.org/10.1002/hed.23434

2 Nishikawa D, Hanai N, Ozawa T, et al. Role of induction chemotherapy for N3 head and neck squamous cell carcinoma. Auris Nasus Larynx 2015;42:150-155. https://doi.org/10.1016/j.anl.2014.10.007

3 Pignon JP, le Maitre A, Maillard E, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4-14. https://doi.org/10.1016/j.radonc.2009.04.014

4 Wahl RL, Jacene H, Kasamon Y, et al. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med 2009;50:122S-1250S. https://doi.org/10.2967/jnumed.108.057307

5 Ballonoff A, Raben D, Rusthoven KE, et al. Outcomes of patients with n3 neck nodes treated with chemoradiation. Laryngoscope 2008;118:995-998. https://doi.org/10.1097/MLG.0b013e31816a7120

6 Karakaya E, Yetmen O, Oksuz DC, et al. Outcomes following chemoradiotherapy for N3 head and neck squamous cell carcinoma without a planned neck dissection. Oral Oncol 2013;49:55-59. https://doi.org/10.1016/j.oraloncology.2012.07.010

7 Jones AS, Goodyear PW, Ghosh S, et al. Extensive neck node metastases (N3) in head and neck squamous carcinoma: is radical treatment warranted? Otolaryngol Head Neck Surg 2011;144:29-35. https://doi.org/10.1177/0194599810390191

8 Porceddu SV, Jarmolowski E, Hicks RJ, et al. Utility of positron emission tomography for the detection of disease in residual neck nodes after (chemo)radiotherapy in head and neck cancer. Head Neck 2005;27:175-181. https://doi.org/10.1002/hed.20130

9 Mehanna H, Wong WL, McConkey CC, et al. PET-CT surveillance versus neck dissection in advanced head and neck cancer. N Engl J Med 2016;374:1444-1454. https://doi.org/ 10.1056/NEJMoa1514493

10 Igidbashian L, Fortin B, Guertin L, et al. Outcome with neck dissection after chemoradiation for N3 head-and-neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2010;77:414-420. https://doi.org/10.1016/j.ijrobp.2009.05.034

11 Moukarbel RV, Fung K, Venkatesan V, et al. The N3 neck: outcomes following primary chemoradiotherapy. J Otolaryngol Head Neck Surg 2011;40:137-142.

12 Mitsudo K, Koizumi T, Iida M, et al. Thermochemoradiation therapy using superselective intra-arterial infusion via superficial temporal and occipital arteries for oral cancer with N3 cervical lymph node metastases. Int J Radiat Oncol Biol Phys 2012;83:e639-645. https://doi.org/ 10.1016/j.ijrobp.2012.02.057

13 Hitt R, Grau JJ, Lopez-Pousa A, et al. A randomized phase III trial

comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. Ann Oncol 2014;25:216-225. https://doi.org/10.1093/annonc/mdt461

14. Cohen EE, Karrison TG, Kocherginsky M, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. J Clin Oncol 2014;32:2735-2743. https://doi.org/10.1200/JCO.2013.54.6309

15. Haddad R, O'Neill A, Rabinowits G, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. Lancet Oncol 2013;14:257-264. https://doi.org/10.1016/S1470-2045(13)70011-1

Geoffrois L, Martin L, De Raucourt D, et al. Induction chemotherapy followed by cetuximab radiotherapy is not superior to concurrent chemoradiotherapy for head and neck carcinomas: results of the GORTEC 2007-02 phase III randomized trial. J Clin Oncol 2018;36:3077-3083.https://doi.org/10.1200/JCO.2017.76.2591

Benasso M, Vigo V, Bacigalupo A, et al. A phase II trial of low-dose gemcitabine and radiation alternated to cisplatin and 5-fluorouracil: an active and manageable regimen for stage IV squamous cell carcinoma of the head and neck. Radiother Oncol 2008;89:44-50.https://doi.org/10.1016/j.radonc.2008.04.002

Gaber P, Primoz S. Combining radiotherapy and immunotherapy in definitive treatment of head and neck squamous cell carcinoma: review of current clinical trials. Radiol Oncol 2020;54:377-393. https://doi.org/10.2478/raon-2020-0060

Tao Y, Auperin A, Graff P, et al. Very accelerated radiotherapy or concurrent chemoradiotherapy for N3 head and neck squamous cell carcinoma: Pooled analysis of two GORTEC randomized trials. Oral Oncol 2017;71:61-66. https://doi.org/10.1016/j.oraloncology.2017.06.002

Liu SA, Tsai WC, Wong YK, et al. Nutritional factors and survival of patients with oral cancer. Head Neck 2006;28:998-1007. https://doi.org/10.1002/hed.20461

Karnell LH, Sperry SM, Anderson CM, et al. Influence of body composition on survival in patients with head and neck cancer. Head Neck 2016;38:E261-267.https://doi.org/10.1002/hed.23983

Gonzalez MC, Pastore CA, Orlandi SP, et al. Obesity paradox in cancer: new insights provided by body composition. Am J Clin Nutr 2014;99:999-1005. https://doi.org/10.3945/ajcn.113.071399

Ko HC, Chen S, Wieland AM, et al. Clinical outcomes for patients presenting with N3 head and neck squamous cell carcinoma: analysis of the National Cancer Database. Head Neck 2017;39:2159-2170. https://doi.org/10.1002/hed.24881

Lassen P, Lacas B, Pignon JP, et al. Prognostic impact of HPV-associated p16-expression and smoking status on outcomes following radiotherapy for oropharyngeal cancer: the MARCH-HPV project. Radiother Oncol 2018;126:107-115. https://doi.org/10.1016/j.radonc.2017.10.018

Supplementary Table I. Uni- and multivariate analysis for regional and locoregional control.

Regional control	Univariate analysis			Multivariate analysis		
	HR	95% IC	p	HR	95% IC	p
Patient parameters						
Sex (male *vs* female)	0.66	(0.20-2.09)	0.477			
Age (> 62 *vs* ≤ 62)	1.15	(0.69-1.92)	0.585			
BMI (< 25 *vs* ≥ 25)	2.59	(1.39-4.81)	**0.003**	3.93	(1.69-9.12)	**0.001**
PS (≥ 2 *vs* 0-1)	3.62	(2.11-6.23)	**< 0.001**	2.60	(1.27-5.33)	**0.009**
Smoking (active vs none or past)	1.18	(0.68-2.06)	0.549			
Hb (< 13.5 or 12.5)	2.05	(1.03-4.05)	**0.039**	1.39	(0.66-2.90)	0.384
Tumour parameters						
Site (others *vs* oropharynx)	0.90	(0.54-1.51)	0.701			
T stage (T3-4 *vs* T1-2)	1.48	(0.86-2.55)	0.161			
N stage (pN3b *vs* pN3a)	0.94	(0.21-4.11)	0.931			
p16 status (pos *vs* neg)	0.37	(0.12-1.12)	0.079			
Treatment						
Surgery *vs* radiotherapy	0.96	(0.55-1.67)	0.894			
Locoregional control	**Univariate analysis**			**Multivariate analysis**		
	HR	95% IC	p	HR	95% IC	p
Patient parameters						
Sex (male *vs* female)	0.57	(0.18-1.83)	0.348			
Age (> 62 *vs* ≤ 62)	1.17	(0.72-1.90)	0.525			
BMI (< 25 *vs* ≥ 25)	2.67	(1.47-4.85)	**0.001**	6.87	(2.01-23.45)	**0.002**
PS (≥ 2 *vs* 0-1)	3.35	(2.01-5.58)	**< 0.001**	1.80	(0.55-5.84)	0.328
Smoking (active *vs* none or past)	1.20	(0.72-2.02)	0.486			
Hb (< 13.5 or 12.5)	1.91	(0.12-3.57)	**0.042**	0.84	(0.19-3.81)	0.826
Tumour parameters						
Site (others *vs* oropharynx)	0.92	(0.57-1.50)	0.741			
T stage (T3-4 *vs* T1-2)	1.50	(0.90-1.51)	0.118			
N stage (pN3b *vs* pN3a)	1.01	(0.23-4.40)	0.992			
p16 status (pos *vs* neg)	0.30	(0.10-0.89)	**0.03**	0.41	(0.07-2.53)	0.337
Treatment						
Surgery *vs* radiotherapy	1.05	(0.62-1.76)	0.857			

Hb: haemoglobin; BMI: body-mass index; PS: performance status.