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Patterns of Failure in Patients With Head and Neck Squamous Cell Carcinomas of Unknown Primary Treated With Chemoradiotherapy

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Abstract

Background: To evaluate the patterns of failure in patients treated for head and neck carcinoma of unknown primary and to discuss treatment practices concerning radiotherapy target volumes definition and dose prescription. **Methods:** Eleven patients presenting a locoregional recurrence after head and neck carcinoma of unknown primary treatment with curative-intent radiochemotherapy performed between 2007 and 2017 in the departments of radiation oncology of 2 French cancer institutes. Images of the computed tomography scan or the magnetic resonance imaging performed at the time of the recurrence were fused with those of the simulation computed tomography scan to delimit a volume corresponding to the recurrence and to define the area of relapse compared to the volumes treated. **Results:** Irradiation was unilateral in 6 cases and bilateral in 5 cases. The median time to onset of recurrence was 7.24 months (extreme 3-67.7 months). Six patients had only a neck node recurrence, 3 had a neck node and subsequent primary recurrence, and 1 had only a median subsequent primary recurrence. Only 1 patient had synchronous distance progression to local recurrence. All neck node recurrences were solitary and ipsilateral. The subsequent primary recurrences were in the oropharynx in 3 cases and in the contralateral oral cavity in one case. All neck node recurrences were into the irradiated volume. The subsequent primary recurrences were either within or in border of the irradiated volumes. The median of the mean dose, received by neck node recurrences, was 69.9 Gy and that of the mean dose, minimum dose, maximum dose, and dose received by 95% of the volume of recurrence was 66.7 Gy. For the primary relapses, the median of the mean dose was 52.1 Gy and that of the mean dose, minimum dose, maximum dose, and dose received by 95% of the volume of recurrence was 39.9 Gy. **Conclusions:** All local nodal recurrences occurred at sites that received high radiotherapy doses and doses received by sites of eventual failure did not vary significantly from sites that remain in control.

Keywords

unknown primary, squamous cell carcinoma, head and neck, chemoradiotherapy, failure

Abbreviations

CT, computed tomography; EBV, Epstein-Barr virus; ^{18}FDG PET, 18 fluoro-deoxyglucose positron emission tomography; HNCUP, head and neck carcinoma of unknown primary; HNSCC, head and neck squamous cell carcinoma; HPV, human papilloma virus; IMRT, intensity-modulated radiotherapy; MRI, magnetic resonance imaging; PTV, planning target volume

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Introduction

Head and neck carcinoma of unknown primary (HNCUP) represents about 3% (1%-5%) of head and neck cancers.[1] Squamous cell carcinomas are observed in 40% of cases, undifferentiated carcinomas in 29% and less frequently adenocarcinomas (27%) and melanomas (7%).[2,3]

The optimal management of this type of tumor is still controversial since no therapeutic strategy has been validated by prospective studies. Many curative therapeutic options have been evaluated in small and heterogeneous retrospective patient series,[4-9] such as exclusive cervical lymph node dissection, cervical lymph node dissection followed by adjuvant radiotherapy, adenectomy (for a small lymph node metastasis), and adjuvant radiotherapy or exclusive radiotherapy and/or chemotherapy (followed in some cases by surgery). The treatment is most often multimodal combining surgery, radiotherapy, and/or concomitant chemotherapy.

Extent of radiotherapy remains an issue of debate. Whether it should be extensive with bilateral cervical lymph node and pharyngeal mucosa irradiation or selective with unilateral cervical lymph node irradiation has not been determined. Indeed, the rate of contralateral lymph node recurrence is low[10-12]; and the emergence of a primary cancer is rare, estimated at 0% to 19%.[8,13,14]

The aim of this retrospective study is to evaluate the patterns of failure after exclusive or adjuvant radiotherapy and chemotherapy in patients treated for HNCUP. We further discuss treatment practices concerning radiotherapy target volumes definition and dose prescription according to relapse areas.

Material and Methods

Population Selection

In this retrospective study, we have consecutively selected all the patients who presented a locoregional recurrence of HNCUP treated between 2007 and 2017 in the departments of radiation oncology of 2 French cancer institutes: Center Georges—François Leclerc in Dijon and Jean Minjoz University Regional Hospital in Besançon. In total, 11 (14.3%) of 77 patients with HNCUP had locoregional recurrence.

The entity "HNCUP" underlines that all routine investigations such as 18 fluoro-deoxyglucose positron emission tomography (^{18}FDG PET) scan and panendoscopy failed to detect the primitive site of the tumor. The disease is thus s into T0 and not Tx (according to the seventh edition of the Tumor node metastasis/International union against cancer (TNM/UICC) 2009 classification of tumors of the head and neck).

Only patients with squamous cell carcinoma were included. Patients with the following criteria were excluded from the study: distant metastasis at the time of diagnosis, prior history of head and neck skin cancer (nonbasal carcinoma), patients referred for palliative radiation therapy, those with a previous history of cervical irradiation, and patients whose disease evolved and presented a distant metastatic mode without local, regional, or locoregional evolution.

Statistical Analysis and Follow-Up

Quantitative and qualitative variables were, respectively, described by calculating median and percentage. The percentage of missing values was also provided.

The following variables were analyzed: sex, age at diagnosis, prior history of tobacco and/or alcohol, weaning or not of tobacco and/or alcohol at the time of diagnosis, histological type, the human papilloma virus (HPV) and Epstein-Barr virus (EBV) status of the initial disease, extracapsular extension, nodal tumor node metastasis (TNM) stage (according to the seventh edition of the TNM/UICC 2009 classification of tumors of the head and neck), number of analyzed and invaded nodes, lymph node size, the site of the lymph nodes according to Gregoire classification,[15-17] neck dissection or not, type of cervical lymph node dissection, extent of cervical irradiation, radiation dose received, overall treatment time, chemotherapy or not, chemotherapy modalities, type of chemotherapy, and number of courses received.

Three months after the end of irradiation, an evaluation was performed. A computed tomography (CT) scan or magnetic resonance imaging (MRI) of the head and neck was required. Complete remission was defined (according to the RECIST 1.1 criteria) as complete disappearance of all initial lesions, partial remission by a decrease in the sum of the longest diameters of initial lesions of $\geq$30% compared with baseline, progression by an increase in the sum of the longest diameter of initial lesions $\geq$20% compared with the smallest-sum longest diameter recorded or the appearance of 1 or more new lesions, and stability by neither complete or partial remission or progression. Local and/or regional recurrence was defined as the first nodal and/or primary tumor relapse in the mucosa of the upper aerodigestive tract, 3 months after the end of treatment, in the region of the head and neck.

Patients were generally seen at regular intervals every 3 to 4 months during the first 3 years, then every 6 months for 2 years and annually thereafter, by a member of a multidisciplinary disease management team consisting of a medical oncologist, a head and neck surgeon, and a radiation oncologist. A CT scan or MRI of the head and neck was required whenever there were suspicious clinical symptoms. In some cases, a PET scan was required.

Our results were based on the analysis of the following variables: number of local and/or regional recurrences, number of new lesions appeared, and delay between the end of treatment and the onset of recurrence.

A rigid image fusion of the CT scan or the MRI performed at the time of the recurrence with the simulation CT scan was performed to delineate a volume corresponding to the recurrence. Thus, it was possible to define the area of relapse compared to the volumes treated (planning target volume [PTV] 50, 54, 66-70 Gy). This was considered to be within the PTV if at least 80% of its volume is included in the treated volume, outside the PTV if 80% of its volume is totally beyond the treated volume, or in the border if the limits overflow for more than 20%. Thereafter, the fusion with the treatment plan

Table 1. Patient Characteristics.

Patient Characteristics	N (%)
Gender	
Men	9 (81.8)
Women	2 (18.2)
Age classes (years)	
<55	2 (18.2)
55-65	4 (36.4)
>65	5 (45.4)
Smoking	
Yes	9 (81.8)
No	2 (18.2)
Smoking weaned at the time of diagnosis	
Yes	3 (33.3)
No	6 (66.7)
Alcoholism	
Yes	7 (63.6)
No	4 (36.4)
Alcoholism weaned at the time of diagnosis	
Yes	3 (42.9)
No	4 (57.1)

Table 2. Tumor Characteristics.

Tumor Characteristics	N (%)
Type of the lymph node metastasis	
Unique	10 (90.9)
Multiple	1 (9.1)
Laterality of the lymph node metastasis	
Unilateral	11 (100)
Bilateral	0 (0)
Histology	
Squamous cell carcinoma	
G1	11 (100)
G2	0 (0)
G3	0 (0)
Nodal TNM stage[a]	
N1	3 (27.2)
N2a	4 (36.4)
N2b	1 (9.2)
N3	3 (27.2)
Site of nodal involvement	
Level Ia	0 (0)
Level Ib	2 (12.5)
Level II	9 (56.2)
Level III	2 (12.5)
Level Iva	1 (6.3)
Level IVb	2 (12.5)

Abbreviation: TNM, tumor node metastasis.
[a]Seventh edition of the TNM/UICC 2009 classification of head and neck tumors.

allowed to calculate the volume (cc) of the recurrence and the dose received (Gy) (mean dose, minimum dose, maximum dose, and dose received by 95% of the volume of recurrence [D95]).

Results

Patients and Tumor Characteristics

Patient and tumor characteristics are summarized in Tables 1 and 2, respectively. Patients were most often men, with a median age at diagnosis of 65 years (range 37-91 years), and most of them were nonweaned of smoking and alcohol at the time of care.

Of the 11 patients, 10 had a solitary lymph node involvement. All of the patients had unilateral involvement, a squamous cell carcinoma in all of cases. The median nodal size was 40 mm (range 12-105 mm). Some large lymph nodes involved more than one nodal level. Level II was the most frequently invaded (56.2%). Seven patients had an involvement of only ipsilateral level II.

Diagnostic Approach and Therapeutic Modalities

Diagnostics consisted of head and neck clinical examination, a panendoscopy of the upper aerodigestive tract, a CT scan supplemented in some cases with an MRI of the head and neck region, an X-ray or chest CT scan, and a routine chemistry. An ^{18}FDG PET scan was performed in 8 (81.8%) patients, showing hypermetabolism other than that of the neck lymph node metastasis in 2 (25%) cases, one in the tonsil and one in the axillary lymph nodes.

Panendoscopy was performed in 10 (90.9%) cases. Among them, one of the 2 patients who had suspicious tonsillar hypermetabolism in the PET scan had a biopsy during the panendoscopy and it was negative. The second patient underwent a biopsy of the suspicious axillary lesion whose malignancy was not confirmed histologically. All patients had cytologically or histologically proven squamous cell carcinomas. Tonsil biopsies were performed in one patient and were negative.

Table 3 summarizes the different treatment modalities.

The majority (63.6%) of patients received unilateral neck dissection. The approach was limited to biopsy in 3 patients with unresectable disease. A mean of 18.5 lymph nodes was analyzed after surgery (range 1-39).

Both HPV and EBV status have been determined retrospectively on the available initial lymph node samples for 5 patients. All samples were negative. All patients were treated with a sliding window intensity-modulated radiotherapy technique (IMRT).

The dose delivered to the PTV "low risk" was 50 Gy. It included bilateral neck lymph nodes from level I to level V (extensive prophylactic irradiation) in 5 patients or ipsilateral neck lymph nodes from level I to level V (selective prophylactic irradiation) in 6 patients.

The dose delivered to the PTV "intermediate risk" was 54 Gy. It included ipsilateral hemimucosa in 6 patients or bilateral in 1 patient.

A dose of 66 to 70 Gy was delivered to the PTV "high risk" defined as the pathologically invaded lymph nodes level(s). The overall median time of irradiation was 48 days (range 46-56 days).

Systemic therapy was administered to 9 (81.8%) patients: It was concomitant to radiotherapy in 8 (72.87%) patients and

Table 3. Treatment Modalities.

Treatment Modalities	N (%)
Lymph nodes surgery	
Yes	8 (72.7)
No	3 (27.3)
Type	
Lymphadenectomy	1 (9.1)
Neck dissection	7 (63.6)
Quality of resection[a]	
R0	2 (18.2)
R1	3 (27.3)
R2	1 (9.1)
Unknown	2 (18.2)
Extracapsular extension	
Yes	6 (54.5)
No	1 (9.1)
Unknown	1 (9.1)
HPV status	
Positive	0 (0)
Negative	5 (45.4)
Unknown	3 (27.3)
EBV status	
Positive	0 (0)
Negative	5 (45.4)
Unknown	3 (27.3)
Radiotherapy	
Target volume	
Ipsilateral neck lymph nodes	4 (36.4)
Ipsilateral neck lymph nodes + mucosa[b]	2 (18.1)
Bilateral neck lymph nodes + ipsilateral mucosa	4 (36.4)
Bilateral neck lymph nodes + mucosa	1 (9.1)
Highest dose prescribed (Gy)	
66	4 (36.4)
70	7 (63.6)
Systemic therapy	
Yes	9 (81.8)
No	2 (18.2)
Modality	
Concomitant	8 (72.7)
Neoadjuvant and concomitant	1 (9.1)
Type	
Cisplatin	7 (63.6)
Carboplatin	1 (9.1)
Erbitux	1 (9.1)
Number of courses	
<3	1 (9.1)
≥3	8 (72.7)

Abbreviations: EBV, Epstein-Barr virus; HPV, human papilloma virus.
[a]R0 indicates complete resection, R1 = microscopic evidence of residual tumor after surgery, R2 = macroscopic evidence of residual tumor after surgery.
[b]Mucosa included nasopharynx and/or oropharynx and/or hypopharynx and/or larynx and/or oral cavity.

neoadjuvant and concomitant in an inoperable patient (9.1%). A weekly cisplatinum-based scheme was usually administered.

Therapeutic Response Evaluation

Radioclinical evaluation, performed 3 months after treatment end, found 6 (54.5%) patients in complete remission, 3 (27.3%) in partial remission, 1 (9.1%) in stabilization, and 1 (9.1%) in progression.

Among the 6 patients who received unilateral irradiation, we found 5 (83.3%) patients in complete remission and 1 (16.7%) in progression. Regarding the 5 patients who received bilateral irradiation, 1 (20%) was in complete remission, 3 (60%) in partial remission, and 1 (20%) in stabilization.

Table 4. Recurrence Evaluation.

Disease Control	Patients (N = 11)	Lesions (N = 14)	
Progression	1	1	
Recurrence(s)	10	13	
		N	Localization
Subsequent primary	1	1	Base of tongue
Neck node	6	6	Ipsilateral
Subsequent primary and neck node	3	6	Ipsilateral neck nodes (3) Subsequent primary: Ipsilateral tonsil (2) Contralateral oral cavity (1)

Recurrence Evaluation

The median time to onset of recurrence was 7.24 months (range 3-67.7 months) and that of primary recurrence was 27.5 months (range 12-68 months). All neck node recurrences were unique and ipsilateral. No patients relapsed in a contralateral lymph node level, including the 6 patients who received unilateral neck node irradiation. One patient had an isolated median subsequent primary recurrence in the base of the tongue. Three patients had a neck node and subsequent primary recurrence. The subsequent primary lesions occurred in the ipsilateral tonsil for 2 patients and in the contralateral oral cavity for a patient (Table 4).

There was only one synchronous distance progression to local recurrence in 1 (9.1%) patient.

In conclusion, there were 9 neck node recurrences (6 isolated and 3 associated with a subsequent primary recurrence) and 4 subsequent primary recurrences, including 3 in the oropharynx and 1 in the oral cavity.

Taking into consideration the different characteristics of the initial disease, neck node recurrences were not related to the initial nodal TNM stage: Only 4 (44.4%) of the 9 neck node recurrences were in patients with advanced-stage disease (≥N2b).

Of the 9 neck node recurrences, 7 appeared in patients who had initially a lymph nodes surgery (a neck dissection for 6 and a lymphadenectomy for 1) and the majority (5/7) was for initial diseases with an extracapsular extension.

Regarding the subsequent primary recurrences, HPV and EBV status for the initial disease were either negative or unknown. On the other hand, HPV status has been determined on the biopsy of one (tonsillar) of these recurrences and was positive when it was unknown for the initial disease. Patient

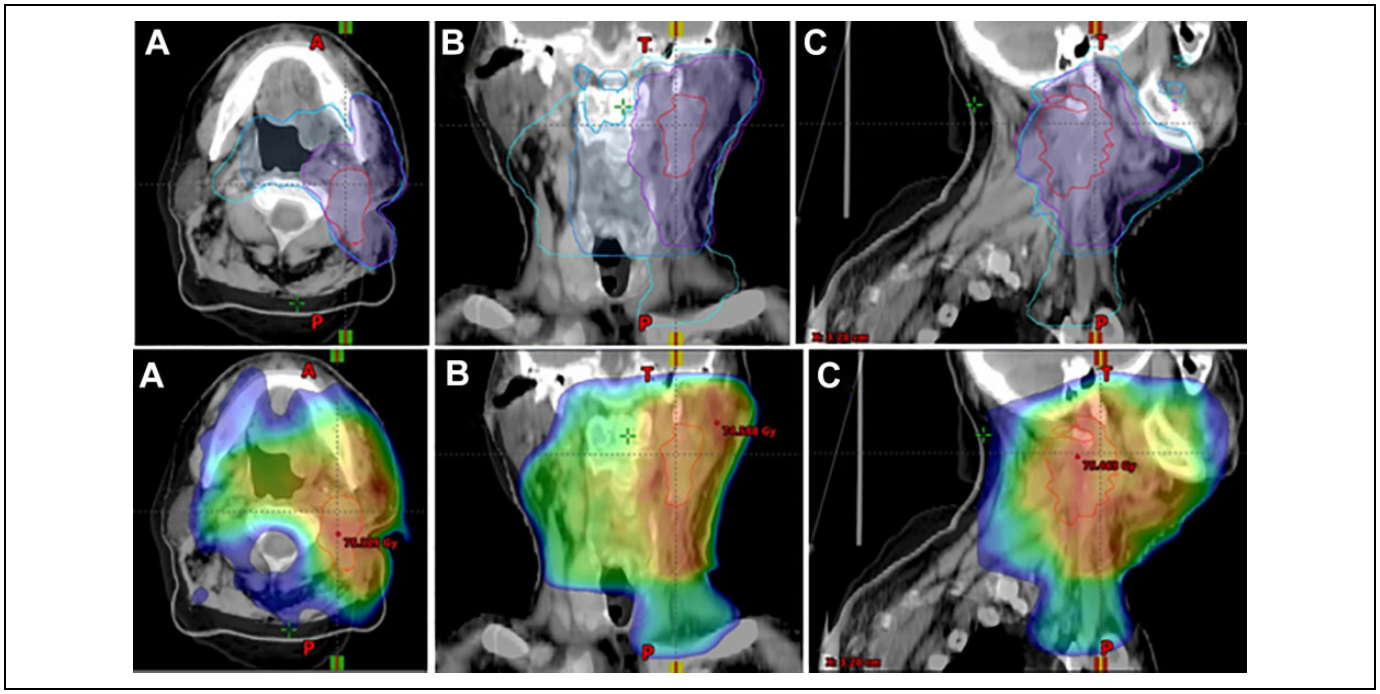

Figure 1. Examples of dosimetric axial (A), coronal (B), and parasagittal (C) scan sections of a patient with a neck node recurrence (delineated in red) within the planning target volume (PTV) 70 Gy (delineated in purple), the PTV 54 Gy (delineated in blue), and the PTV 50 Gy (delineated in cyan).

who progressed had an initial disease classified as N2a and was treated exclusively by extensive radiotherapy.

All neck node recurrences occurred inside the irradiated volume. Of the 9 neck node recurrences, 5 were even within the PTV 66 to 70 Gy and 4 were in border of this volume. Thus, they were systematically in the ipsilateral prophylactic neck lymph node-irradiated volume (50 Gy). No neck node recurrence is found in the contralateral prophylactic neck node volume (Figure 1).

Regarding subsequent primary recurrences, 75% were in border of the PTV 66 to 70 Gy. All of them were either within (50%) or in border (50%) of the prophylactic neck node volume (50 Gy). One recurrence was in the contralateral PTV "low risk." For the only patient who progressed locally and received a prophylactic irradiation of the hemimucosa, recurrence overlapped in border of the PTV "intermediate risk" (54 Gy; Figure 2).

Irradiation extent (selective or extensive) had no impact on the sites of recurrences regarding the initial target volumes and the dose received by the recurrence ($P = 1.00$).

Dosimetric analysis at the neck node recurrences showed a median of mean dose of 69.9 Gy (extreme 60.3-72.7 Gy), a median of minimum dose of 57.7 Gy (extreme 0-68.3 Gy), a median of maximum dose of 73 Gy (extreme 68.3-75.5 Gy), and a median of D95 of 66.7 Gy (extreme 13.8-71 Gy). The median volume of the neck node recurrences was 30.6 cc (extreme 0.9-99.5 cc; Table 5).

For subsequent primary relapses, the median of the mean dose was 52.1 Gy (extreme 42.7-66.1 Gy), the median of the minimum dose was 24.6 Gy (extreme 4-42.6 Gy), the median of the maximum dose was 69.5 Gy (extreme 66.9-73.5 Gy) and that of the D95 was 39.9 Gy (extreme 12.9-54.4 Gy). The median volume of subsequent primary relapses was 35.7 cc (extreme 18.8-57 cc; Table 5).

Discussion

The management of patients with HNCUP remains controversial. Therapeutic strategies range from an exclusive surgical resection to a multimodal approach consisting in a neoadjuvant chemotherapy and radiotherapy or postoperative chemoradiotherapy. In the absence of prospective randomized trials, retrospective studies have shown that in patients with low risk of recurrence after neck node dissection, in particular those who had an histologically confirmed N1 or N2a disease without extracapsular extension, an exclusive neck node dissection was sufficient to disease control.[18,19] However, in the presence of poor prognostic factors, such as a more advanced-stage disease with extracapsular extension, neck node dissection followed by adjuvant radiotherapy or chemoradiotherapy is increasingly becoming the therapeutic standard.[13] One of the most controversial topics concerning radiotherapy is the irradiation volume.

The definition of the target volume in radiotherapy remains a subject of debate due to conflicting results on different studies comparing selective versus extensive. The purpose of irradiating pharyngeal mucosa is simply to treat undetectable primitive tumors.

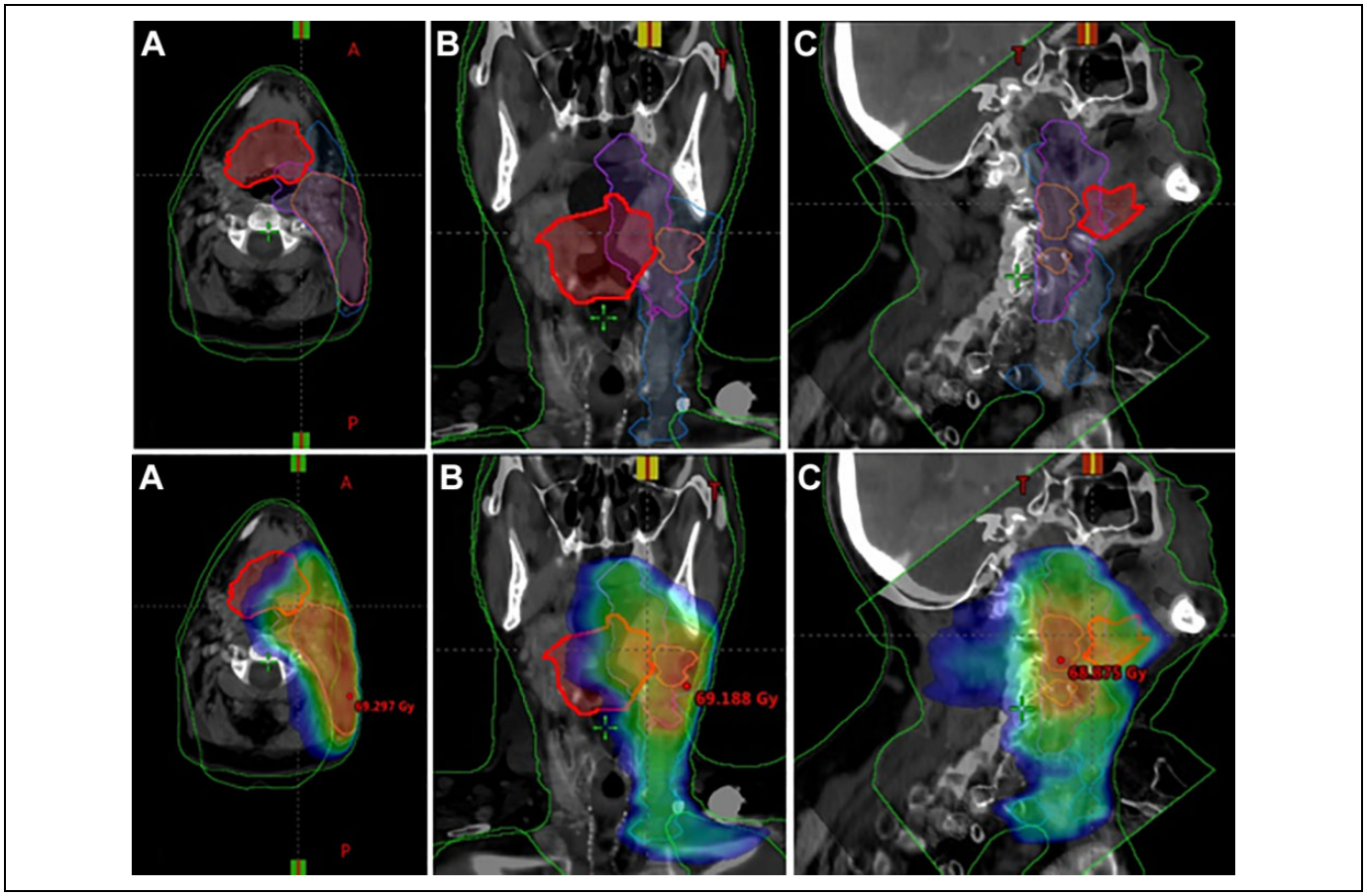

Figure 2. Examples of dosimetric axial (A), coronal (B), and parasagittal (C) scan sections of a patient with an oropharyngeal subsequent primary recurrence (delineated in red) outside the planning target volume (PTV) 66 Gy (delineated in orange) and in border of the PTV 54 Gy (delineated in purple), and the PTV 50 Gy (delineated in blue).

Table 5. Dosimetric Analysis at the Recurrences Sites.

Dose Received by the Site of Recurrence	Neck Node Recurrences	Subsequent Primary Relapses
Mean dose (Gy)		
Median	69.9	52.1
Extreme	60.3-72.7	42.7-66.1
Minimum dose (Gy)		
Median	57.7	24.6
Extreme	0-68.3	4-42.6
Maximum dose (Gy)		
Median	73	69.5
Extreme	68.3-75.5	66.9-73.5

Our study addressed a possible relationship between the patterns of locoregional failure and the dose prescribed to different target volumes in patients treated with radiotherapy for HNCUP. The aim was to determine whether these relapses were related to underdosing or conversely whether areas with a low risk of recurrence were overtreated. If the latest was observed, consideration could be given to reducing target volumes or de-escalating doses at these levels.

In our series, 9 patients had a neck node recurrence and 1 had progressed at the end of radiotherapy. All these recurrences were unique and ipsilateral. No patients relapsed in a contralateral lymph node area, including the 6 patients who received unilateral neck node irradiation.

Four subsequent primary mucosal relapses were diagnosed during the follow-up: 3 in the ipsilateral oropharynx and 1 in the contralateral oral cavity.

Results of the different retrospective studies comparing unilateral with bilateral cervical irradiation were heterogeneous.

Several authors have recommended bilateral irradiation of neck node areas and pharyngeal mucosa, showing an improvement in locoregional control rate, contralateral neck node relapse rate, and appearance of subsequent primary tumor in the pharyngeal mucosa rate.[5,7,20] The MD Anderson Cancer Centre showed excellent results after bilateral irradiation and whole pharyngeal mucosa, with a 5-year regional control rate of 96% if initially there was a unique neck node involvement and 86% when it was multiple. The rate of subsequent primary mucosal tumors emergence was 8%. Forty-two points (8%) of these subsequent primary recurrences were located in unirradiated tissues. Only 1 patient had contralateral neck node

Table 6. Site of Neck Node Recurrences According to the Irradiation Extent.

Study	Number of Neck Node Recurrences	Site of Neck Node Recurrence			
		Ipsilateral		Contralateral	
		Selective Irradiation	Extensive Irradiation	Selective Irradiation	Extensive Irradiation
Reddy *et al*[8]	26	3	11	7	5
Glynne-Jones *et al*[22]	12	8	3	1	–
Marcial-Vega *et al*[23]	13	3	7	–	3
Our study	9	4	5	–	–

Table 7. Subsequent Mucosal Primary Recurrences According to the Irradiation Extent.

Study	N	Subsequent Primary Recurrences	
		Selective Irradiation	Extensive Irradiation
Grau *et al*[2]	30	3/26 (11.5%)	17/224 (7.5%)
Reddy *et al*[8]	10	7/16 (44%)	3/36 (8%)
Weir *et al*[21]	7	6/85 (7%)	1/59 (1.6%)
Glynne-Jones *et al*[22]	3	2/34 (9%)	1/9 (11%)
Our study	4	2/6 (33%)	2/5 (40%)

recurrence.[6] However, the benefit of extensive radiotherapy should be assessed according to acute and late toxicities of extensive irradiation, including IMRTs. Moreover, in the context of neck node or primary mucosal recurrence in irradiated fields, salvage surgical treatment and/or re-irradiation may be compromised. As a result, more selective neck node and pharyngeal mucosa irradiation is commonly practiced.

Other studies did not demonstrate a significant difference in local control between selective or extensive irradiation, with a median local relapse rate ranging from 31% to 63% after unilateral irradiation[2,6,8,21-23] compared to a median local relapse rate of 8% to 49%, after bilateral irradiation and pharyngeal mucosa.[9,19,22-28]

Table 6 summarizes the results of some retrospective studies as well as our findings in terms of neck node recurrences sites according to irradiation extent.

Similarly, Ligey *et al*[10] showed that neck node relapse rate was 34% after unilateral neck node irradiation and 25% after a bilateral one ($P = .21$).

Marcial-Vega *et al*[23] analyzed results from 80 patients and were not able to show a significant impact of the target irradiation volumes enlargement on the rate of subsequent primary mucosal tumors emergence as well as on the 5-year survival. Similarly, Weir *et al*[21] showed a rate of subsequent primary mucosal recurrences of 7% in 85 patients who received unilateral irradiation, compared to 2% of 59 who had bilateral irradiation. The overall 5-year neck node relapse rate was 49% and the 5-year survival rate was 41%. In their multivariate analysis, there was no difference in survival between the 2 groups.

Table 7 summarizes the results of some retrospective studies as well as our findings in terms of subsequent mucosal primary recurrences according to the irradiation extent.

According to our results, most recurrences appeared within or near initial radiation fields (91.6%). All neck node recurrences were inside or in border of the PTV "high risk." Similarly, 75% of primary recurrences were into or adjacent to PTV 66 to 70 Gy and all were within or in contact with PTV 50 Gy.

Moreover, this was confirmed by the dosimetric analysis with a median of the mean dose, received by neck node recurrences, of 69.9 Gy and a median of the D95 of 66.7 Gy. For the primary mucosal relapses, the median of the mean dose was 52.1 Gy and that of the D95 was 39.9 Gy.

Similarly, Cuaron *et al*[11] demonstrated that the doses prescribed to sites of eventual failure did not vary significantly from those sites that were treated and remain in control. Indeed, an extensive irradiation has been considered each time an advanced initial disease and poor prognostic factors are present. This could increase the percentage of relapses observed even in the context of extensive irradiation and skew results.

In conclusion, it seems that there is no relationship between the risk of locoregional failure of HNCUP and the dose or the volume of irradiation. This has led to think that other factors could negatively impact the locoregional control, such as the initial nodal TNM stage, extracapsular extension, and HPV status of the initial disease.

According to our results, neck node recurrences were not related to the initial nodal TNM stage: Only 44.4% arose in patients with advanced-stage disease ($\geq$N2b). Seventy-one points (4%) of the neck node recurrences occurred in patients who were initially operated for initial lesions with extracapsular extension.

Extracapsular extension has been reported in approximately 60% of regional metastasis of HNSCCs.[29,30] A significant relationship has been demonstrated between extracapsular extension and the emergence of contralateral neck lymph node metastasis.[31] It has also been shown that an extracapsular extension of less than 1 mm is associated with a better prognosis than an extracapsular extension $\geq$2 mm.[32]

A strong relationship between extracapsular extension and lymph node stage has been demonstrated in a large cohort study.[33] Extracapsular extension was noted in 35% of patients with neck node disease classified as N1, 55% N2, and 74% N3. The presence or absence of extracapsular extension was strongly correlated with the size of lymph node metastasis, with an incidence of 69% in lymph node metastasis greater than 3 cm and 39% in those less than 3 cm.[34]

Regarding tumor HPV status, several recent multiinstitutional prospective analyses have shown this as an important

and independent prognostic factor for progression-free survival and overall survival in patients who have oropharyngeal cancer.[35-37] Oropharyngeal "HPV +" carcinomas seem to have a better prognosis than the "HPV−" ones. Given the favorable prognosis, the possibility of therapeutic de-escalation in HNSCC "HPV+" was discussed.

In our study, HPV status has been retrospectively determined on the initial available lymph node samples for 5 patients. All samples were negative. Of these 5 patients, 3 had a subsequent primary mucosal recurrence (2 in the tonsil and 1 in the base of tongue). The HPV status has been determined only on the biopsy of a tonsillar recurrence and was positive.

The lack of data did not allow us to find a relationship between the HPV status and the patterns of failure of HNCUP. Through a systematic review of the literature conducted by Boscolo-Rizzo *et al*,[38] positivity for HPV markers in HNCUP was a strong predictor of the emergence of a primary occult tumor in the oropharynx and one of the favorable prognostic indicators for this type of cancer. These results confirm that HPV status should be systematically evaluated in patients who have HNCUP, to identify a possible undetectable primary tumor and to limit prophylactic mucosal irradiation to the oropharynx mucosa in an "HPV+" carcinoma.

All these data contributed to the definition of a new TNM classification for HNCUP (eighth edition of the TNM/UICC 2017 classification of head and neck tumors) by taking into account the degree of extracapsular extension and the tumor HPV and EBV status, which could modify therapeutic management of patient with HNCUP.[39]

Our study has some limits related its retrospective nature. Despite the fact that, to our knowledge, our study is one of the largest HNCUP series in terms of relapses, the number of patients included was not enough to achieve statistical significance.

Conclusion

Innovative techniques, including IMRT, allowed optimization of HNCUP management leading to good locoregional control and less toxicities. Doses prescribed to sites of eventual failure did not vary significantly from sites that were treated and remain in control. According to our results, all the local nodal recurrences occurred at sites that received high radiotherapy doses. Substantial changes in the prognostic TNM 2017 classification should lead to a reevaluation of strategies, based on extracapsular extension and tumor HPV and EBV status.

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Ethical Statement

Our study did not require an ethical board approval because it did not contain human or animal trials.

Declaration of Conflicting Interests

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References

1. Zhou MJ, van Zante A, Lazar AA, et al. Squamous cell carcinoma of unknown primary of the head and neck: favorable prognostic factors comparable to those in oropharyngeal cancer. *Head Neck*. 2018;40(5):904-916.
2. Grau C, Johansen LV, Jakobsen J, Geertsen P, Andersen E, Jensen BB. Cervical lymph node metastases from unknown primary tumours: results from a national survey by the Danish Society for Head and Neck Oncology. *Radiother Oncol*. 2000;55(2):121-129.
3. Galloway TJ, Ridge JA. Management of squamous cancer metastatic to cervical nodes with an unknown primary site. *J Clin Oncol*. 2015; 33(29):3328-3337.
4. Aslani M, Sultanem K, Voung T, Hier M, Niazi T, Shenouda G. Metastatic carcinoma to the cervical nodes from an unknown head and neck primary site: is there a need for neck dissection? *Head Neck*. 2007;29(6):585-590.
5. Beldi D, Jereczek-Fossa BA, D'Onofrio A, et al. Role of radiotherapy in the treatment of cervical lymph node metastases from an unknown primary site: retrospective analysis of 113 patients. *Int J Radiat Oncol Biol Phys*. 2007;69(4):1051-1058.
6. Colletier PJ, Garden AS, Morrison WH, Goepfert H, Geara F, Ang KK. Postoperative radiation for squamous cell carcinoma metastatic to cervical lymph nodes from an unknown primary site: outcomes and patterns of failure. *Head Neck*. 1998;20(8): 674-681.
7. Erkal HS, Mendenhall WM, Amdur RJ, Villaret DB, Stringer SP. Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head and neck mucosal site treated with radiation therapy alone or in combination with neck dissection. *Int J Radiat Oncol Biol Phys*. 2001;50(1):55-63.
8. Reddy SP, Marks JE. Metastatic carcinoma in the cervical lymph nodes from an unknown primary site: results of bilateral neck plus mucosal irradiation vs. ipsilateral neck irradiation. *Int J Radiat Oncol Biol Phys*. 1997;37(4):797-802.
9. Strojan P, Anicin A. Combined surgery and postoperative radiotherapy for cervical lymph node metastases from an unknown primary tumour. *Radiother Oncol*. 1998;49(1):33-40.
10. Ligey A, Gentil J, Créhange G, et al. Impact of target volumes and radiation technique on loco-regional control and survival for patients with unilateral cervical lymph node metastases from an unknown primary. *Radiother Oncol*. 2009;93(3):483-487.
11. Cuaron J, Rao S, Wolden S, et al. Patterns of failure in patients with head and neck carcinoma of unknown primary treated with radiation therapy: patterns of failure in head and neck carcinoma

of unknown primary treated with RT. *Head Neck*. 2016;38(suppl 1):E426-E431.
12. Perkins SM, Spencer CR, Chernock RD, et al. Radiotherapeutic management of cervical lymph node metastases from an unknown primary site. *Arch Otolaryngol Head Neck Surg*. 2012;138(7): 656-661.
13. Troussier I, Klausner G, Morinière S, et al. Évolutions dans la prise en charge des métastases ganglionnaires cervicales sans Cancer primitif retrouvé; avancées diagnostiques et nouvelle classification TNM. *Bull Cancer* .2017;20(5):492-503.
14. Klem ML, Mechalakos JG, Wolden SL, et al. Intensity-modulated radiotherapy for head and neck cancer of unknown primary: toxicity and preliminary efficacy. *Int J Radiat Oncol*. 2008;70(4): 1100-1107.
15. Gregoire V, Ang K, Budach W, et al. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. *Radiother Oncol*. 2014;110(1):172-181.
16. Gregoire V, Eisbruch A, Hamoir M, Levendag P. Proposal for the delineation of the nodal CTV in the node-positive and the postoperative neck. *Radiother Oncol*. 2006;79(1):15-20.
17. Gregoire V, Levendag P, Ang KK, et al. CT based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC, RTOG consensus guidelines. *Radiother Oncol*. 2003;69(3):227-236.
18. Coster JR, Foote RL, Olsen KD, Jack SM, Schaid DJ, DeSanto LW. Cervical nodal metastasis of squamous cell carcinoma of unknown origin: indications for withholding radiation therapy. *Int J Radiat Oncol Biol Phys*. 1992;23(4):743-749.
19. Harper CS, Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Cancer in neck nodes with unknown primary site: role of mucosal radiotherapy. *Head Neck*. 1990;12(6):463-469.
20. Iganej S, Kagan R, Anderson P, et al. Metastatic squamous cell carcinoma of the neck from unknown primary: management options and patterns of failure. *Head Neck*. 2002;24(3):236-246.
21. Weir L, Keane T, Cummings B, et al. Radiation treatment of cervical lymph node metastases from an unknown primary: an analysis of outcome by treatment volume and other prognostic factors. *Radiother Oncol*. 1995;35(3):206-211.
22. Glynne-Jones RG, Anand AK, Young TE, Berry RJ. Metastatic carcinoma in the cervical lymph nodes from an occult primary: a conservative approach to the role of radiotherapy. *Int J Radiat Oncol Biol Phys*. 1990;18(2):289-294.
23. Marcial-Vega VA, Cardenes H, Perez CA, et al. Cervical metastases from unknown primaries: radiotherapeutic management and appearance of subsequent primaries. *Int J Radiat Oncol Biol Phys*. 1990;19(4):919-928.
24. Bataini JP, Rodriguez J, Jaulerry C, Brugere J, Ghossein NA. Treatment of metastatic neck nodes secondary to an occult epidermoid carcinoma of the head and neck. *Laryngoscope*. 1987; 97(9):1080-1084.
25. Maulard C, Housset M, Brunel P, et al. Primary cervical lymph nodes of epidermoid type. Results of a series of 123 patients treated by the association surgery-radiotherapy or irradiation alone. *Ann Otolaryngol Chir Cervicofac*. 1992;109(1):6-13.
26. Davidson BJ, Spiro RH, Patel S, Patel K, Shah JP. Cervical metastases of occult origin: the impact of combined modality therapy. *Am J Surg*. 1994;168(5):395-399.
27. Lefebvre JL, Coche-Dequeant B, Van JT, Buisset E, Adenis A. Cervical lymph nodes from an unknown primary tumor in 190 patients. *Am J Surg*. 1990;160(4):443-446.
28. Nguyen C, Shenouda G, Black MJ, Vuong T, Donath D, Yassa M. Metastatic squamous cell carcinoma to cervical lymph nodes from unknown primary mucosal sites. *Head Neck*. 1994;16(1):58-63.
29. Johnson JT, Barnes EL, Myers EN, et al. The extracapsular spread of tumors in cervical node metastasis. *Arch Otolaryngol*. 1981; 107(12):725-729.
30. Johnson JT, Myers EN, Bedetti CD, Barnes EL, Schramm VL, Jr, Thearle PB. Cervical lymph node metastases: incidence and implications of extracapsular carcinoma. *Arch Otolaryngol*. 1985;111(8):534-537.
31. Suoglu Y, Erdamar B, Katircioglu OS, Karatay MC, Sunay T. Extracapsular spread in ipsilateral neck and contralateral neck metastases in laryngeal cancer. *Ann Otol Rhinol Laryngol*. 2002;111(5 pt 1):447-454.
32. Keller LM, Galloway TJ, Holdbrook T, et al. p16 status, pathologic and clinical characteristics, biomolecular signature, and long-term outcomes in head and neck squamous cell carcinomas of unknown primary: HPV-associated SCC of unknown primary. *Head Neck*. 2014;36(12):1677-1684.
33. Pinsolle J, Pinsolle V, Majoufre C, Duroux S, Demeaux H, Siberchicot F. Prognostic value of histologic findings in neck dissections for squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg*. 1997;123(2):145-148.
34. Carter RL, Barr LC, O'Brien CJ, Soo KC, Shaw HJ. Transcapsular spread of metastatic squamous cell carcinoma from cervical lymph nodes. *Am J Surg*. 1985;150(4):495-499.
35. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363(1):24-35.
36. Rischin D, Young RJ, Fisher R, et al. Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 phase III trial. *J Clin Oncol*. 2010;28(27):4142-4148.
37. Lassen P, Eriksen JG, Hamilton-Dutoit S, Tramm T, Alsner J, Overgaard J. Effect of HPV-associated p16INK4A expression on response to radiotherapy and survival in squamous cell carcinoma of the head and neck. *J Clin Oncol*. 2009;27(12): 1992-1998.
38. Boscolo-Rizzo P, Schroeder L, Romeo S, Pawlita M. The prevalence of human papillomavirus in squamous cell carcinoma of unknown primary site metastatic to neck lymph nodes: a systematic review. *Clin Exp Metastasis*. 2015;32(8):835-845.
39. Troussier I, Klausner G, Blais E, et al. Advances in the management of cervical lymphadenopathies of unknown primary with intensity modulated radiotherapy: doses and target volumes. *Cancer Radiother*. 2018;22(5):438-446.