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; 18FDG 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. Squamous cell carcinomas are observed in 40% of cases, undifferentiated carcinomas in 29% and less frequently adenocarcinomas (27%) and melanomas (7%).

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, 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, and the emergence of a primary cancer is rare, estimated at 0% to 19%.

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 (18FDG 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, 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 ≥30% compared with baseline, progression by an increase in the sum of the longest diameter of initial lesions ≥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...
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 18FDG 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 involved 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 (72.8%) patients and

| 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<sup>a</sup>      |       |
| 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.
<sup>a</sup>Seventh edition of the TNM/UICC 2009 classification of head and neck tumors.
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.

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
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. 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. 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.
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 latter 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. 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 involvement.

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                  |

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

| Study                | Number of Neck Node Recurrences | Site of Neck Node Recurrence | Study | Number of Neck Node Recurrences | Site of Neck Node Recurrence |
|----------------------|---------------------------------|-----------------------------|-------|---------------------------------|-------------------------------|
|                      | Selective Irradiation | Extensive Irradiation | Selective Irradiation | Extensive Irradiation |
| Reddy et al²         | 26                              | 3                           | 11     | 7                               | 5                             |
| Glynne-Jones et al²² | 12                              | 8                           | 3      | 1                               | –                             |
| Marcial-Vega et al²³ | 13                              | 3                           | 7      | –                               | 3                             |
| Our study            | 9                               | 4                           | 5      | –                               | –                             |

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

| Study                        | N Selective Irradiation | Extensive Irradiation |
|------------------------------|--------------------------|------------------------|
| Grau et al²                  | 30                       | 3/26 (11.5%)           |
| Reddy et al²                 | 10                       | 7/16 (44%)             |
| Weir et al²¹                 | 7                        | 6/85 (7%)              |
| Glynne-Jones et al²²         | 3                        | 2/34 (9%)              |
| Our study                    | 4                        | 2/6 (33%)              |

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.

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 (≥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. A significant relationship has been demonstrated between extracapsular extension and the emergence of contralateral neck lymph node metastasis. It has also been shown that an extracapsular extension of less than 1 mm is associated with a better prognosis than an extracapsular extension ≥2 mm.

A strong relationship between extracapsular extension and lymph node stage has been demonstrated in a large cohort study. 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.

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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