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Impact of waiting time on nodal staging in head and neck squamous-cell carcinoma treated with radical intensity modulated radiotherapy

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ABSTRACT

Background and purpose: To evaluate the influence of delays for radiotherapy on survival, recurrence and upstaging for head and neck squamous-cell carcinoma (HNSCC) with no nodal involvement treated with intensity modulated radiotherapy (IMRT).
Material and methods: This retrospective study included 63 consecutive patients with HNSCC located in the pharynx and larynx and treated with exclusive IMRT with or without chemotherapy. Survival, loco-regional or distant failure and upstaging were analyzed according to the waiting time.
Results: Mean waiting time for treatment was 62.5 days for the hypopharynx subgroup (range = 37–102), 63 days for the larynx subgroup (range = 19–128) and 58.5 days for the oropharynx subgroup (range = 29–99) ($p = 0.725$). Nine patients (14%) experienced upstaging. Loco-regional or distant failure occurred in 18 patients. Beyond a delay of 50 days, 19% of patients had local failure, 17% nodal recurrence and 11% distant failure. Within a delay of 50 days, no nodal or distant failure was observed and only 1 patient experienced local recurrence. Upstaging and overall survival were not significantly affected by an increased waiting time.
Conclusion: For N0 patients treated with IMRT for HNSCC, waiting time around 50 days after the diagnosis was not significantly associated with an excessive risk of upstaging or recurrence.

Waiting time in radiotherapy is a major issue as it might affect the prognosis of patients suffering from head and neck squamous-cell carcinoma (HNSCC) [1]. The delay to diagnosis [2] and to treatment can be prolonged by several factors such as dental care, comorbidities or advanced age [1,3]. Increased waiting time can result in upstaging of the tumor [4] and might affect tumor local control and patients' survival [5–7]. Nowadays, as intensity modulated radiation therapy (IMRT) is widely used for patients suffering from HNSCC, the prolonged treatment planning due to delineation of the target volumes and organs at risks, treatment planning optimization and quality assurance procedures increase the waiting time preceding the start of the treatment. Even though a recent study conducted in the Netherlands did not show impaired survival in patients treated for HNSCC within a delay of 90 days [8], potential tumor progression during these periods was not studied [8,9] in the era of IMRT. Recent guidelines from the French Ear Nose and Throat Society (SFORL) recommend a delay no greater than four weeks between the first consultation and the beginning of any treatment [10,11]. In the ongoing EORTC-1219 trial, it is recommended to start radiotherapy within 8 weeks from baseline imaging assessment and ideally 2 weeks (4 weeks maximum) after randomization.

In this retrospective study, which focused on patients suffering from HNSCC without nodal involvement during the staging procedure, we aimed to determine whether our local practice was in agreement with the national recommendations and the impact of delays on outcomes.

Materials and methods

Selection of patients and definitions

Between January 2007 and December 2013, the medical records of patients treated with exclusive radiotherapy or radio-

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chemotherapy in Dijon Comprehensive Cancer Center were reviewed. We extracted sex, age, tumor characteristics, date of pathological diagnosis, site of tumor, TNM staging, treatment modalities, tumor recurrence and death. In order to evaluate the impact of waiting time on nodal staging, patients with proven HNSCC without nodal involvement at the time of diagnosis and treated with exclusive radiotherapy or radio-chemotherapy were included. Exclusion criteria were oral cavity cancer, neo-adjuvant chemotherapy or surgery as the first treatment and patients who did not receive prophylactic nodal irradiation or who had distant metastasis. Recurrence was divided into local, nodal and distant. Local recurrence was defined as failure occurring within the Clinical Target Volume (CTV). Nodal recurrence was defined as recurrence in the regional lymph node areas whether they had received prophylactic irradiation or not. Distant recurrence was defined as any metastasis, excluding regional lymph node metastasis.

Treatment delay was measured as the interval between the date of the pathological diagnosis and the date of the first fraction of radiotherapy. Patients started their treatment before 14 days after planning CT. TNM staging (AJCC 7th edition) [12] evaluated during a multidisciplinary team meeting was collected for each patient and re-evaluated on the planning CT. Upstaging was defined as a modification of the TNM stage evaluated on the planning CT and/or with a clinical examination when available. Nodal involvement was judged significant when the short axis was greater than 10 mm [13,14]. Both T and N upstaging were taken into account during the delineation process. Overall survival was defined as the time from pathological diagnosis to death from any cause. The primary objective of our work was to investigate, in N0 patients, the impact of an increased delay to treatment on outcomes and upstaging before treatment measured as a TNM modification as well as recurrence, distant control and survival. The secondary objective of this study was to compare our practices with national and international recommendations.

Statistical analysis

Categorical variables are described as percentages and continuous variables are presented as means (with standard deviations, SD) and medians (with ranges). Comparisons between groups were performed using a Chi2 or Fisher test for qualitative variables and a non-parametric Kruskal-Wallis test for quantitative variables. Survival probabilities were estimated using the Kaplan-Meier method and the log-rank test was used to compare survival curves. Statistical analyses were performed using SAS 9.3 software. All tests were two sided and p values were considered significant when less than 0.05.

Results

Upstaging and recurrence

Patients' characteristics are summarized in Table 1. Sixty-three consecutive patients (89% of men) were eligible. There were 14 hypopharyngeal cancers, 23 laryngeal cancers and 26 oropharyngeal cancers. Median age was 61 years old (range = 42–87). The

Table 1
Patients' characteristics and treatment.

	Hypopharynx (n = 14)		Larynx (n = 23)		Oropharynx (n = 26)	
	n	%	*n*	%	*n*	%
Age						
n	14		23		26	
Mean (STD)	61.3 (9.3)		64.4 (11.1)		58.6 (10.1)	
Median (min-max)	61.5 (47–75)		64 (42–83)		58 (45–87)	
Sex						
Male	13	92.9%	22	95.7%	21	80.8%
Female	1	7.1%	1	4.3%	5	19.2%
Initial T stage						
1	1	7.1%	2	8.7%	6	23.1%
2	5	35.7%	13	56.5%	11	42.3%
3	5	35.7%	7	30.4%	8	30.8%
4	3	21.4%	1	4.3%	1	3.8%
Initial N stage						
0	14	100.0%	23	100.0%	26	100.0%
Planning CT updated T stage						
1	1	7.1%	2	8.7%	6	23.1%
2	4	28.6%	13	56.5%	10	38.5%
3	5	35.7%	7	30.4%	8	30.8%
4	4	28.6%	1	4.3%	2	7.7%
Planning CT updated N stage						
0	11	78.6%	23	100.0%	23	88.5%
1	3	21.4%	0	0.0%	3	11.5%
Simultaneous integrated boost						
No	8	57.1%	14	60.9%	12	46.2%
Yes	6	42.9%	9	39.1%	14	53.8%
Concurrent chemotherapy						
No	6	42.9%	13	56.5%	21	80.8%
Yes	8	57.1%	10	43.5%	5	19.2%
Duration						
n	14		23		26	
Mean (STD)	45.1 (6.7)		46.2 (4.4)		44.8 (6.4)	
Median (min-max)	48 (32–56)		46 (39–56)		44.5 (26–56)	

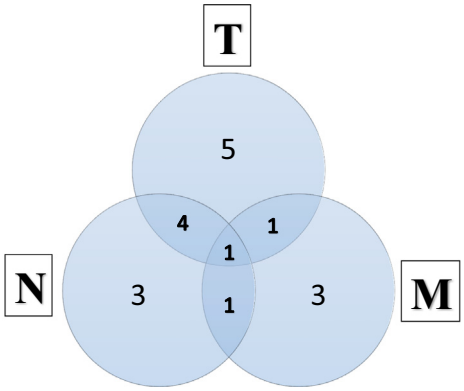

Fig. 1. Patterns of failure.

most frequent stages were T2 or T3 (71% for the hypopharynx, 87% for the larynx and 73% for the oropharynx). The greatest proportion of T4 stage was in the hypopharynx subgroup with 21.4% of patients, compared with 4.3% and 3.8% respectively in the larynx and oropharynx subgroups. Among the four patients with stage T4 in the hypopharynx subgroup, two had an extension to the esophagus and two an extension through the thyroid cartilage. All of them declined surgery. Regarding treatment modalities, a Simultaneous Integrated Boost (SIB) technique was used for 34 patients (54%). Twenty-three patients (36.5%) received concurrent chemotherapy, with 3 cycles of Cisplatin. Median follow-up was respectively 41 months (range = 19–NA) for the hypopharynx, 47 months (range = 29.6–56.5) for the larynx and 42 months (range = 23–61) for the oropharynx ($p = 0.48$). The 2- and the 5-year OS (Fig. 2) were 71% and 22% for the hypopharynx subgroup, 90% and 32% for the larynx subgroup and 84% and 61% for the oropharynx subgroup, respectively.

Upstaging was observed in four patients in the hypopharynx subgroup (36%) and five patients in the oropharynx subgroup (19%). No upstaging was noted in the larynx subgroup. Four patients had a T upstage and six underwent nodal upstaging, exclusively N1 disease. One patient experienced both a T and N upstage. Among the four patients with tumor upstaging, two belonged to the hypopharynx subgroup and two to the oropharynx subgroup. Among the five patients who experienced isolated nodal upstaging, three were in the hypopharynx subgroup and two in the oropharynx subgroup. One patient in the hypopharynx subgroup experienced both tumor and nodal upstaging.

Failures occurred in 18 patients (28.5%): four in the larynx subgroup (17%), seven in the oropharynx subgroup (27%) and seven in the hypopharynx subgroup (50%). The distribution between local, nodal and distant failure is shown in Fig. 1. Among the 11 patients with local recurrence (17%), three were in the hypopharynx subgroup (21%), four in the oropharynx subgroup (15%) and four in the larynx subgroup (17%). Nodal failure (nine patients, 14%) was the most common site of failure for pharyngeal cancers as it occurred in 20% of the cohort: three patients in the hypopharynx subgroup (21%) and five patients in the oropharynx subgroup (19%). Only one patient (4.3%) suffering from laryngeal cancer had a nodal recurrence. Finally, distant metastasis (six patients, 9.5%) was preponderant in the hypopharynx group accounting for 28.6% of distant failures, compared with 3.8% and 4.3% for the oropharynx and larynx group, respectively.

Among the 18 patients with failures only two (11%) experienced upstaging prior to the beginning of treatment. Of these two patients, one had both local and nodal recurrence and the other had distant failure.

Impact of waiting time on recurrence and upstaging

Median waiting time for treatment was 62.5 days for the hypopharynx subgroup (range = 37–102), 63 days for the larynx subgroup (range = 19–128) and 58.5 days for the oropharynx subgroup (range = 29–99) ($p = 0.72$). Two patients started their treatment after a delay of less than 30 days and 52 after a delay of 50 days or more. No patient experienced upstaging between planning CT and the first fraction. The median waiting time for patients with an upstaged tumor was 59.5 days (range = 48–66). Beyond a delay of 50 days, three patients (6%) had tumor progression and six (11.5%) had nodal progression. There was no significant difference regarding the median waiting time for patients with or without tumor upstaging prior to treatment ($p = 0.67$). The median time for treatment was not significantly different between patients who

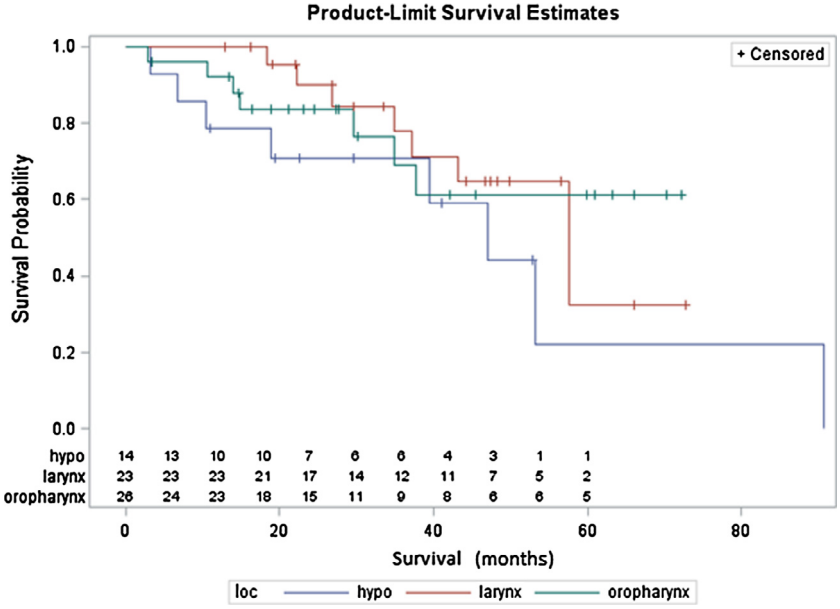

Fig. 2. Overall survival according to subgroups.

Table 2
Patterns of failure according to waiting time.

Waiting time	Yes		No		*p*
	n	%	*n*	%	
Local failure					
<30	0	0.0%	2	100.0%	1
⩾30	11	18.0%	50	82.0%	
<50	1	9.1%	10	90.9%	0.6714
⩾50	10	19.2%	42	80.8%	
Nodal failure					
<30	0	0.0%	2	100.0%	1
⩾30	9	14.8%	52	85.2%	
<50	0	0.0%	11	100.0%	0.3393
⩾50	9	17.3%	43	82.7%	
Distant metastasis					
<30	0	0.0%	2	100.0%	1
⩾30	6	9.8%	55	90.2%	
<50	0	0.0%	11	100.0%	0.5792
⩾50	6	11.5%	46	88.5%	

experienced nodal upstaging and those who did not (58.5 days (range = 51–99) and 61 days (range = 19–128), respectively ($p = 0.97$)).

Only one local recurrence (9%) and no regional or distant failure were observed for patients who started their treatment within 50 days (Table 2). With a waiting time beyond 50 days, 10 patients had a local recurrence (19%) ($p = 0.67$), nine had regional failure (17%) ($p = 0.34$) and six distant failure (11.5%) ($p = 0.58$). Overall survival was not significantly impaired in patients who waited more than 50 days for treatment (Fig. 3).

Impact of upstaging on outcomes

In our study, upstaging was not associated with a significantly higher rate of loco-regional or distant failure. No patients with laryngeal cancer underwent a modification of their staging before the start of their treatment. In our cohort, nine patients (14%) experienced upstaging, including four upstages for the primary tumor and 6 for the lymph nodes (one patient had both). Likewise, overall survival was not significantly different for patients experiencing upstaging.

Discussion

Recent guidelines of the SFORL [10,11] stated that patients should be treated within 30 days after the first appointment. In our study, only 2 patients over 63 were treated within this given timeframe. This long delay might be due to several factors such as the time to obtain the complete histopathological status including viral markers, additional examinations or time to organize the simulation procedure on the dedicated CT scanner, the time required to prepare a complex radiation treatment. In our setting, most of patients are referred for treatment after the preliminary diagnostic procedure. The delay between diagnosis and the first appointment in our center is thus out of our control. Frequently, additional imaging procedures are mandatory to complete the work-up process. A Danish study published in 2006 showed an increased delay of treatment of almost 3 weeks between 1992 and 2002, mostly attributable to an increased number of imaging procedures preceding the preparation of treatment [15]. Everyone involved in the management of these patients should be informed about the potential impact of prolonged waiting times on outcomes in order to improve the global care of patients.

Due to the routine use of IMRT, which is more complex to set up, new critical steps such as specific treatment planning, plan evaluation or quality assurance for treatment verification have led to longer delays before initiating the treatment [16]. To our knowledge, this is the first report to evaluate practices in the era of IMRT. In this setting, the time to delineate target volumes has been tripled [17]. To reduce the delineation process, some teams are developing algorithms for automatic delineation of organs at risk and lymph node areas to speed up the clinical time [18–20]. The time required by medical physicists has also increased with the implementation of new algorithms and inversed-planned IMRT techniques [21]. Quality assurance at each step of the preparation, whether it concerns treatment planning, the delivery system or is patient-specific, is mandatory to provide the required level of quality [22–24]. Nevertheless, treatment preparation cannot be

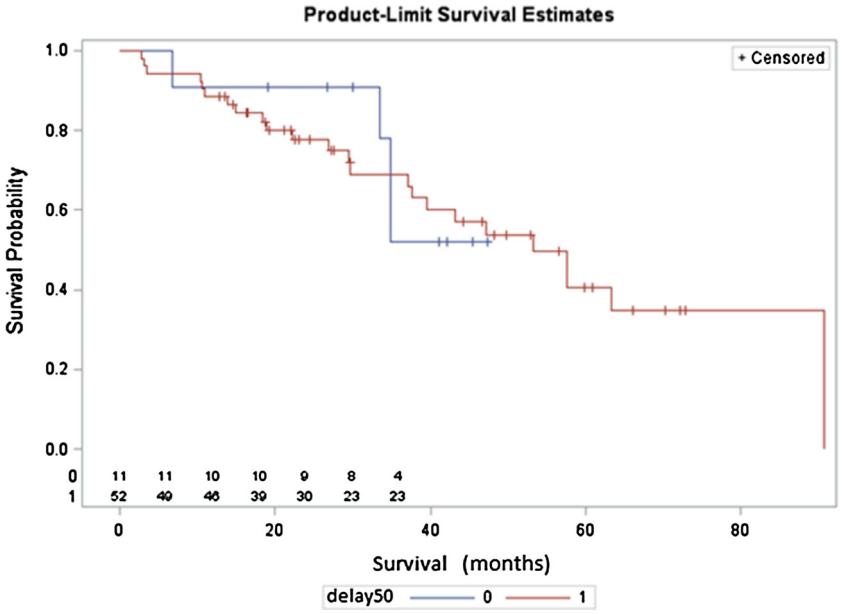

Fig. 3. Overall survival according to waiting time. 50 days.

excessively shortened as there is a risk of decreasing the safety of the treatment delivery [25]. Given the increasing numbers of patients amenable to radiotherapy and the emerging indications, waiting lists for simulation scans are lengthening. A Danish team created a model for managing patients' bookings with different waiting times. This allowed the better management of patients who needed a short preparation time [26]. It was demonstrated that waiting times can be reduced with logistic changes in the way patients are managed in the different departments involved [27]. According to our results, some adjustments for HNSCC can be applied for patients without nodal involvement.

When facing an upstaged patient, the strategy should be re-examined in multidisciplinary meetings, during which more extensive radiotherapy or the addition of concomitant chemotherapy has to be discussed. These modifications could increase the risk of acute or late toxicities, and thus significantly impair patients' quality of life. This aspect was not evaluated in our study [28]. Our study, unlike other studies, did not show an increased risk of upstaging with increased waiting time [4,29]. These reports date back to 2007 and 2001, respectively. Our population was highly selected with only N0 patients at the diagnosis, and more recent work-up procedures as well as more accurate delineation of the target volumes are improving the efficiency of radiotherapy. Finally, upstaging is not an accurate evaluation of tumor progression. In this selected population of N0 patients, however, the N upstaging remains a relevant tool. Nevertheless, upstaged patients suffering from N0 HNSCC treated with IMRT did not have a higher risk of local, regional or distant failure. Consequently, in this setting, overall survival was not degraded.

The impaired survival in hypopharyngeal cancer can be explained by the poorer prognosis for this primary tumor [30], the greater proportion of patients with advanced stage in this subgroup and the small sample size (14 patients). In our study, even though a non-significant increased risk of failure was observed in the subgroup who waited more than 50 days, prolonged waiting times before radiotherapy was not detrimental as regards the risk of local, regional or distant failure. These findings are not consistent with other retrospective reviews of the literature [4–6]. The absence of significant results was mostly due to the small sample size and low power despite the absolute difference in recurrences seen between the subgroups treated within 50 days following diagnosis and those treated beyond 50 days.

Conclusion

Practices with regard to our studied population did not match either national or international recommendations for treatment delays in radiotherapy. Modifications in the organization of departments and patient management processes need to be implemented so as not to impair patients' prognosis. In the era of IMRT, which requires a long period of careful preparation, a waiting time around 50 days was not significantly associated with an excessive risk of a poor outcome. The N0 criteria at inclusion and a small sample size prevented our results to reach significance.

Conflict of interest

None.

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