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ORIGINAL ARTICLE

The risk of recurrence in surgically treated head and neck squamous cell carcinomas: a conditional probability approach

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ABSTRACT

Background: Over 50% of patients with head-and-neck squamous cell carcinoma (HNSCC) experience locoregional recurrence, which is associated with poor outcome. In the course of follow-up for patients surviving primary surgery for HNSCC, one might ask: What is the probability of recurrence in one year considering that the cancer has not yet recurred to date?

Materials and methods: To answer this question, 979 patients surgically treated for HNSCC (i.e. cancer of the oral cavity, oropharynx, hypopharynx or larynx) between March 2004 and June 2018 were enrolled in a multicenter retrospective cohort study, followed up for death and recurrence over a 5 year period. The conditional probability of recurrence in 12 months – i.e. the probability of recurrence in the next 12 months given that, to date, the patient has not recurred – was derived from the cumulative incidence function (Aalen-Johansen method).

Results: Overall, the probability of recurrence was the highest during the first (17.3%) and the second years (9.6%) after surgery, declining thereafter to less than 5.0% a year thereafter. The probability of recurrence was significantly higher for stage III–IV HNSCCs than for stage I–II HNSCCs in the first year after surgery (20.4% versus 10.0%; $p < 0.01$), but not thereafter. This difference was most pronounced for oral cavity cancers. No significant differences were observed across different tumor sites.

Conclusion: This dynamic evaluation of recurrence risk in patients surgically treated for HNSCC provides helpful and clinically meaningful information, which can be useful to patients in planning their future life, and to clinicians in tailoring post-treatment surveillance according to a more personalized risk stratification.

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Head and neck cancers; survival; recurrence; conditional probability; squamous cell carcinoma

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the 6th most common cancer worldwide, with 890,000 new cases documented every year, and 450,000 deaths in 2018 [1,2]. HNSCC is a heterogeneous disease that includes cancers arising from the epithelial linings of the oral cavity, pharynx, and larynx. The survival rate for these neoplasms differs according to anatomical site: in Europe, 5-year overall survival is 59% for the larynx, 45% for oral cavity, 39% for the oropharynx, and 25% for the hypopharynx [3]. In addition to site, stage at diagnosis is an important predictor of both survival and recurrence following treatment with curative intent [4]. Recurrence is most likely to occur within the first 2 years following treatment, and a patient is generally considered to be disease-free after 5 years without recurrence [5]. For HNSCC, the early detection of mucosal failure as well as second primary tumors is a key point in follow-up programs with the aim of improving overall survival [6].

Cancer recurrence is usually considered as a cumulative probability of tumor relapse over a given time period, with reference to the date of diagnosis [2]. Although this information is crucial in planning the therapeutic approach at the time of diagnosis, it becomes less useful as patients survive.

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Table 1. Characteristic of study population.

Patient characteristic	No.	(%)	(95% Confidence interval)
Sex			
Male	712	72.7	(69.8–75.5)
Female	267	27.3	(24.5–30.2)
Age (years			
<60	285	29.1	(26.3–32.1)
60–69	357	36.5	(33.4–39.6)
≥70	337	34.4	(31.4–27.5)
Cancer site			
Oral cavity	409	41.8	(38.7–44.9)
Oropharynx	135	13.8	(11.7–16.1)
Hypopharynx	61	6.2	(4.8–7.9)
Larynx	374	38.2	(35.1–41.3)
Tumor size[a]			
T1	103	10.8	(8.9–13.0)
T2	344	36.1	(33.0–39.2)
T3	222	23.3	(20.6–26.1)
T4	284	29.8	(26.9–32.8)
Lymph nodes[a]			
N0	480	53.6	(50.3–56.9)
N1	125	14.0	(11.8–16.4)
N2–N3	290	32.4	(29.3–35.6)
TNM stage[a]			
I–II	292	30.2	(27.3–33.2)
III	210	21.7	(19.1–24.4)
IV	466	48.1	(45.0–51.3)
Extra–capsular extension[a]			
Absent	639	81.2	(78.3–83.9)
Present	148	18.8	(16.1–21.7)
Margins[a]			
Negative	647	71.3	(68.2–74.2)
Close	141	15.5	(13.2–18.1)
Positive	120	13.2	(11.1–15.6)
Adjuvant (chemo)–radiotherapy[a]			
No	470	48.4	(45.2–51.5)
Yes	502	51.6	(48.5–54.8)
Smoking status[a]			
Current	468	53.1	(49.7–56.4)
Former	219	24.8	(22.0–27.8)
Never	195	22.1	(19.4–25.0)
Alcohol Status[a]			
Current	240	29.3	(26.2–32.6)
Former	90	11.0	(8.9–13.3)
Never	489	59.7	(56.3–63.1)

[a]The sum does not add up to total because of missing values.

The risk of recurrence in one year is different for a newly diagnosed cancer patient compared to one who has survived two years. Dynamic evaluation of oncological outcomes is a need shared by clinicians and patients. From a clinical point of view, this information may be useful to tailor follow-up programs, in addition to specific recurrence rates and whether earlier detection of recurrence leads to increased rates of successful salvage treatment. For patients, the actual probability of recurrence at a specific time in their disease history may be helpful in alleviating anxiety and allowing planning of their future life.

Conditional probability is the most appropriate method to answer these questions. This method is most often employed in the form of survival analysis (usually Kaplan–Meier functions), which makes use of the product of all conditional probabilities of non-recurrence calculated at each event, up to the time point under consideration (i.e. the product-limit method) [7]. However, if instead the conditional probabilities are calculated within pre-defined time-spans (similar to the actuarial method) and without the above cumulative technique, one can answer a different and more clinically relevant question: 'What is a patient's probability of recurrence in a given year, knowing that, to date, they have not recurred?' Thus, the conditional probability model is the most appropriate approach to estimate the risk of recurrence, as ascertainment of recurrence is not continuous, but rather it occurs at scheduled consultations (time points) during the follow-up program [8].

The aim of this study was therefore to define the risk of recurrence at given time-points in the post-treatment surveillance of patients surgically treated for HNSCC, by taking into account the prior information of a tumor's non-recurrence. This information could be more clinically relevant than standard cumulative probability estimates.

Methods

Study design

We conducted a multicenter retrospective cohort study on 1001 consecutive patients diagnosed with HNSCC who underwent surgical treatment between March 2004 and June 2018 in eight Italian centers (Brescia, Ferrara, Padova, Pavia, Pordenone, Treviso, Trieste, and Verona). Population size in the catchment area and period of enrollment varied according to study centers, thus impacting on accrual rate. On average, the accrual rate was 15 patients/year, ranging from 9 to 35 patients/year according to study center. Exclusion criteria included: (a) alive patients without recurrence and less than 12-month follow-up, since they were excluded from the calculation to avoid bias; (b) patients with nasopharyngeal cancer or with metastatic disease; (c) patients with a previous cancer history other than non-melanoma skin cancer; (d) patients who did not undergo surgical treatment. Of the 1001 patients, 22 patients were excluded due to lack of information about recurrence and/or mortality, thus leaving 979 eligible patients of the following sites: oral cavity ($n = 409$), oropharynx ($n = 135$), hypopharynx ($n = 61$), and larynx ($n = 374$). Patient demographics and tumor characteristics included age, gender, tobacco and alcohol consumption, tumor site, tumor TNM stage (7th Edition), tumor grade, and HPV status (for oropharyngeal cancer). Data concerning surgery included date of surgery, margin status, presence of extra capsular extension, and pathological TNM staging. In all centers, the treatment was compliant with NCCN guidelines for head and neck cancer. The routine follow-up program consisted of a locoregional examination at 6–10-week intervals during the first year, 3-month intervals in the second year, 4–6-month intervals between the third and fifth year. Imaging of the primary tumor and the neck (computed tomography and/or magnetic resonance imaging) was performed 8–12 weeks after treatment; a chest radiograph or computed tomography was performed annually. Recurrence was defined as clinical or imaging evidence of tumor, nodal, or metastatic relapse or second primary tumor arising in the head and neck, esophagus or lung. The study was approved locally by all participating centers and data were anonymized by each center.

Statistical analysis

For each patient the time at risk was calculated from the date of surgery to the date of recurrence, death or last follow-up, whichever occurred first, and then expressed in years. Patients were censored when they were lost to follow-up or they died during the observation period.

The risk of recurrence was analyzed using the conditional probability of recurrence (R) at a chosen time point *t*, calculated as the probability of recurrence given that the cancer has not recurred (NR) in the years before *t*.

The Aalen-Johansen estimator [9] was used to provide the estimate for the cumulative incidence function and the corresponding confidence intervals, by taking into account the competing risk of death. Once calculated, the difference in probability between *t* and *t-1* allowed the derivation of the conditional probability of growth within a given year, taking into account the competing risk of death. Using this methodology, analyses were also undertaken using time-intervals of 2- and 3-years, with patients censored when lost to follow-up or deceased during the relevant time-interval. Nominal data were analyzed using χ^2 test with Yates continuity correction. Data analyses were undertaken using Python Version 3.8.2 (Python Software Foundation) with packages *SciPy* and *lifelines*.

Results

Patients' characteristics are listed in Table 1. Overall 979 patients were included in the study. Median age at diagnosis was 65 years (range: 26–92 years) and the majority of patients were males (72.7%). Oral cavity and larynx were the most prevalent sites accounting for 41.8and 38.2% of all HNSCC, respectively. Seventy percent of cancers were diagnosed at stage III–IV with 51.6% of all patients undergoing post-operative adjuvant (chemo)-radiotherapy. Of the 979 patients included in the recurrence analyses over the whole 5-year period, 337 patients (34.4%; 95% CI: 31.4–37.5%) showed recurrence. Over the 5-year period, 322 (32.9%; 95% CI: 33.9–40.1%) patients died, 178 (55.3%; 95% CI: 49.7–60.8%) of them after having experienced a recurrence. The probability of recurrence in one year intervals was the highest during the first (17.3%) and the second years (9.6%) after surgery, declining to below 5.0% each year thereafter (Table 2). The probabilities of recurrence using the 2- and 3-year intervals were 26.8% and 31.6% after one year from surgery, respectively (Table 2). These risks continued to decline as the length of time from surgery increased, reaching 47.5% and 10.7% after 3 years from surgery.

Site

Across the whole 5-year period, recurrences were most commonly observed among cancers of the hypopharynx (49.1%; 95% CI: 35.6–62.7%) and oral cavity (36.8%; 95% CI: 32.0–41.8%). The cumulative incidences of recurrence by tumor site are shown in Figure 1(a). No significant differences in recurrence rates among different tumor sites were recorded, neither across the whole 5-year period, nor in each of the first 5 years of follow-up. Nonetheless, probability of recurrence in the first year was the highest for hypopharyngeal cancer (27.1%; 95% CI: 16.6–38.8%), but the CIs were wide due to the low number of cases.

Stage

Across the whole 5-year period, cumulative incidence of recurrence was significantly higher for stage III-IV (39.2%, 95% CI: 35.4–43.1%) than for stage I–II 26.9% (95% CI: 21.9–32.5%; $p<0.01$). The conditional probability of recurrence (i.e. the difference between cumulative incidences in two consecutive years) was significantly higher for stage III–IV than for stage I–II HNSCCs in the first year (20.4%; 95% CI: 17.4–23.6% versus 10.0%; 95% CI: 6.9–13.8%; $p<0.01$ – Figure 1(b)), but not thereafter.

Site and stage

Since the probability of recurrence likely depends on both tumor site and stage, the analysis was also conducted for both these factors in combination (Table 3). Among oral cancers, frequency of recurrence in the whole 5-year period was lower in stage I–II (27.6%; 95% CI: 20.5–35.6%) than in stage III–IV (42.7%; 95% CI: 36.4–49.1%; $p<0.01$). The conditional probability of recurrence (derived from Aalen-Johansen estimates) was significantly higher for stage III-IV than for stage I-II (24.8% versus 11.5%, $p<0.01$) in one year, but not thereafter.

The 5-year recurrence frequency for laryngeal cancer was similar in stage I–II 23.4% (95% CI: 15.7–32.5%) and stage III–IV 35.5% (95% CI: 29.5–41.7%; $p>0.05$) cancers as well as for any year following surgery.

The 5-year recurrence prevalence for oropharyngeal cancers was similar for stage I–II (37.5%; 95% CI: 21.1–56.3%) and stage III–V tumors (33.3%; 95% CI: 24.3–43.4%; $p=0.97$). A different pattern of recurrence seemed to emerge for late and early stage oropharyngeal cancers. Indeed, conditional probability of recurrence declined with time from surgery for the former, but not for the latter (Table 3). Confidence intervals were however too wide to draw any conclusion. The hypopharynx group was not included in the statistical analysis because of insufficient data.

Discussion

The current study represents a multicentre analysis of recurrence following surgical treatment of HNSCC using conditional probability. Our findings confirmed that regardless of HNSCC subsites, the rate of recurrence is highest in the first two years after treatment [4]. In addition, we found that regardless of tumor site, patients who did not relapse in the first 2 years had a reduction in the risk of recurrence in the following years to less than 5%. Predictably, our results also showed that patients with advanced stage disease at presentation have higher recurrence rates than those with early stage disease; this holds true only for the first year following

Table 2. Cumulative recurrence rate and conditional probability of recurrence in one, two, and three years according to years following surgery.

		Conditional probability of recurrence		
Years following surgery	Cumulative recurrence-rate[a] % (95% CI)	In 1 year	In 2 years	In 3 years
1	17.3 (14.9–19.7)	17.3%	26.8%	31.6%
2	26.8 (24.1–29.7)	9.6%	14.3%	17.1%
3	31.6 (28.6–34.6)	4.8%	7.5%	10.7%
4	34.3 (31.3–37.4)	2.8%	5.9%	–
5	37.5 (34.2–40.8)	3.2%	–	–

[a]Adjusted for competing risk according to the Aalen–Johansen method.
CI: confidence interval.

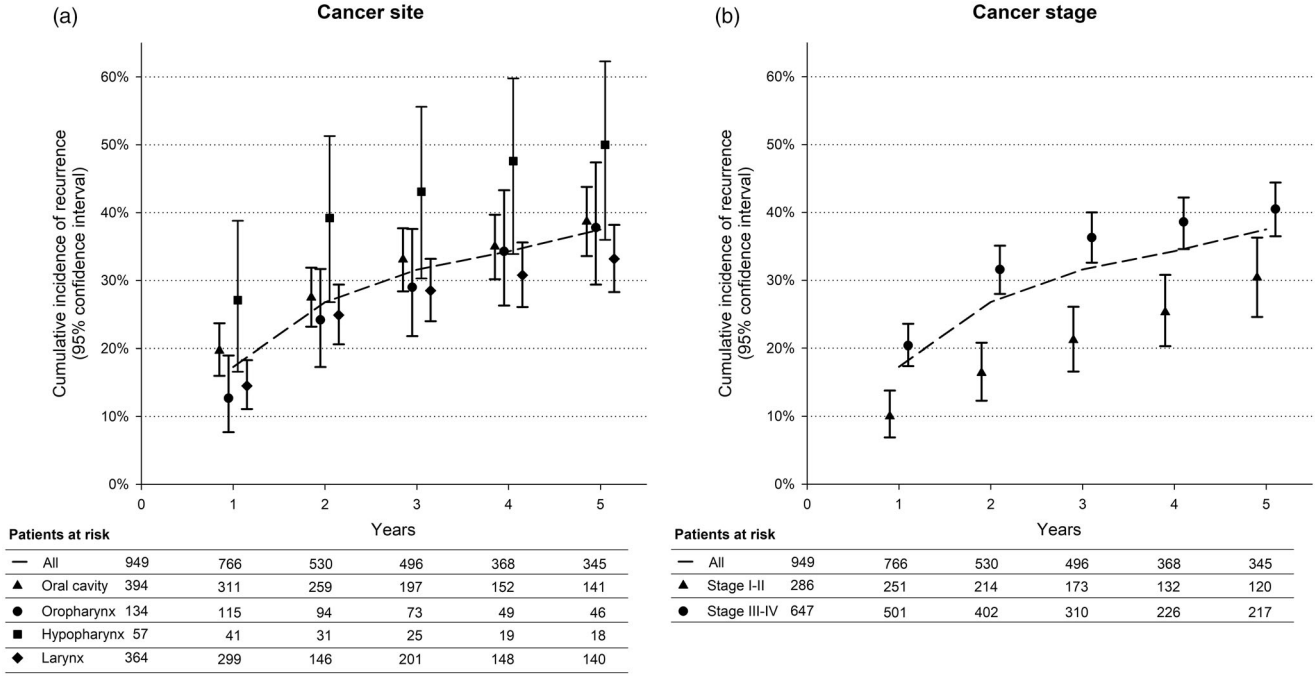

Figure 1. Cumulative incidence of recurrence (Aalen–Johansen method) and corresponding 95% confidence interval according to cancer site (a) and stage (b).

Table 3. Conditional probability of recurrence[a] and corresponding 95% confidence intervals (CI) by cancer site and stage.

	Conditional probability of recurrence					
	Oral cavity		Oropharynx		Larynx	
	Stage I–II	Stage III–IV	Stage I–II	Stage III–IV	Stage I–II	Stage III–IV
Patients	150	255	32	103	108	260
Years following surgery						
1	11.5%	24.8%	9.4%	13.8%	8.3%	16.9%
2	4.9%	9.5%	9.4%	12.1%	7.5%	12.0%
3	5.2%	5.7%	3.9%	5.3%	4.9%	3.4%
4	3.7%	1.1%	12.0%	2.8%	2.7%	2.6%
5	6.3%	2.1%	8.5%	1.8%	1.6%	2.1%

[a]Derived from cumulative incidence, adjusted for competing risk according to the Aalen-Johansen method.

treatment and is most marked in the case of oral cavity cancer.

Recurrence in HNSCC, particularly local recurrence, is unfortunately common and represents a therapeutic challenge. The cause of the high incidence of local recurrences in HNSCC is still unclear. It may be due to multiple malignant and pre-malignant lesions as a consequence of field cancerization of the extensive portion of the mucosal surface of the upper aerodigestive tract [10,11]. About 10%-15% of patients who have locoregional failure can be salvaged by surgery or re-irradiation; indeed, timely diagnosis is crucial as patients with recurrence diagnosed at an early stage have the best chance of cure. Moreover, treatment of recurrence leads to enduring functional impairment in most patients [12]. Thus, even if cure remains achievable, locoregional recurrence may have a significantly negative impact on patients' quality of life [13]. Estimating the individual risk of tumor recurrence may ease personalized diagnostic follow-up strategies designed to detect recurrence at a stage when curative treatments can be used. Indeed, there is a significant worldwide discrepancy regarding the optimal surveillance strategy following treatment of HNSCC [14], and clinicians must plan surveillance schedules based on perceived risk of recurrence.

In the context of cancer treatment, conditional probability provides different information than the standard cumulative recurrence rates; in fact, the former are static estimates that

rely upon patient and tumor characteristics at the time of diagnosis, and they do not fully consider that the risk of recurrence changes as the time from diagnosis elapses. Thus, the cumulative 5-year recurrence rates are useful at the time of diagnosis, rather than during follow-up. Indeed, patients frequently enquire about their chances of cancer recurrence at post-treatment surveillance appointments. For this purpose, a conditional probability approach to cancer recurrence has the advantage of allowing temporal localization of the outcome of interest using baseline characteristics together with the information that the patient has not recurred up to the point of estimation. The ideal model would include all tumor, patient and treatment characteristics known to influence prognosis; however, this approach would require a very large sample size, so for the purpose of this study, we focused on the two most important prognostic discriminators, i.e. tumor site and stage [15].

Conditional survival was firstly described in the context of HNSCC survival in 2007 using SEER data [16], finding that the 5-year overall survival rose significantly in the first three years following diagnosis, plateauing thereafter. They concluded that conditional survival was a potentially useful tool in estimating prognosis in HNSCC patients surviving more than one year after treatment, so that conditional probability of survival was applied for the implementation of an individualized prediction tool [17]. In contrast to Wang and colleagues [17], we focused on recurrence as whilst survival following cancer treatment is clearly the overall priority, in the clinical setting the early detection of recurrence is key to improving outcomes.

Conditional probability has previously been used with Korean Cancer Registry data [18] to estimate 5-year overall survival at specific time-points after oral cancer diagnosis, taking into account that a patient has survived until that time-point. However, a 5-year span is too long to tailor surveillance strategies to individual risk. Therefore, our analysis focused on 1-year recurrence risk, for each of the first five years following treatment. This gives more useful information to both the patient and the clinician, and it carries the potential advantage of using this technique to help plan surveillance strategies following treatment.

The analysis employed here differs from two other main methodologies used for conditional probability in survival analysis. The actuarial method [19] is based on the assumption that censored patients withdraw randomly throughout the interval and that they have a 50% risk of recurrence. This method would thus bias toward higher probabilities of recurrence. Further, the concept of withdraw does not hold for disease-free survival as a patient may not be aware of a recurrence, which can be confirmed only by imaging. The other main methodology, Kaplan–Meier method [7], applies the same principles as the actuarial method, but the conditional probabilities of survival are estimated every time a recurrence occurs (i.e. data are not grouped in pre-fixed time intervals). When applying this method for time intervals, patients censored between t and t_{-1} would be included in the denominator of the probability, and these censored patients would be taken away only in the subsequent period (t_{+1}). This approach would therefore assume that those who are censored do not exhibit recurrence in that time interval, which would bias results toward lower probabilities of recurrence. By using the Aalen-Johansen estimator, the conditional probability approach takes into account the competing risk of death, which does not influence the estimates of the recurrence probability.

Some limitations have to be acknowledged. First, the power to investigate the effect of large numbers of variables on conditional probability of recurrence is limited by the sample size. Several factors may affect the risk of recurrence and prognosis in patients with HNSCC, such as age, smoking and drinking status, HPV status, surgical tumor margins, and adjuvant treatment. However, given the sample size limitation, we were able to consider only site and stage, which are the most important outcome predictors; however, future research will require a larger sample size in order to incorporate all predictors of outcome, including genetic ones. This will allow a shift toward a personalized patients' stratification into groups able to predict the risk of recurrence based on genetic, environmental, and clinical factors. Further, the conditional approach did not allow to account for potential confounders through multivariable analyses. Nonetheless, stratification by relevant covariates (e.g., cancer site, stage) may provide accurate estimates. Finally, selection bias may have occurred due to the retrospective nature of this study. However, all consecutive patients who underwent to surgery in the collaborating centers were evaluated for inclusion, thus limiting this source of bias.

Conclusions

This analysis found that the risk of recurrence after a HNSCC was highest in the first two years after treatment and declined thereafter. Differently from the commonly used 5-year cumulative recurrence rates, which are useful at the time of diagnosis, the proposed analysis provides a dynamic evaluation of the recurrence risk estimates. These data provide clinically meaningful information to personalized surveillance programs after curative treatment (e.g., in terms of the intensity of follow-up diagnostic strategies) as the time after initial treatment elapses.

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Author contributions

DB, MS, JF, and PBR conceived the study; MS performed the statistical analysis; JP provided advice on statistical issues; DB, MiT, AD, PN, PB, CF, GM, DM, MaT, FC, GT, AC, SP, VC, PC, MB, VL, VG, DC, LB, AM, and GC collected the original data; RO and JF provided expertise in the interpretation of the results; DB, MS, JF, JP and PBR drafted the manuscript; all the authors critically revised the manuscript and approved the final version.

Disclosure statement

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