Competing risks analysis of cause-specific mortality in patients with oral squamous cell carcinoma

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ABSTRACT: *Background.* Survival studies on head and neck cancers are frequently reported with inadequate account for competing causes of death. Realistic descriptions and predictions of postdiagnosis mortality should be based on proper competing risks methodology.

Methods. Prognosis of patients with oral squamous cell carcinoma (OSCC) in terms of mortality from OSCC and from other causes, respectively, was analyzed according to recent methodological recommendations using cumulative incidence functions and models for cause-specific hazards and subdistribution hazards in 306 patients treated in a tertiary care center in Northern Finland.

Results. More coherent and informative descriptions and predictions of mortality by cause were obtained with state-of-the-art statistical methods for competing risks than using the prevalent but questionable practice to graph "disease-specific survival."

Conclusion. From the patients' perspective, proper competing risks analysis offers more relevant prognostic scenarios than naïve analyses of "disease-specific survival"; therefore, it should be used in prognostic studies of head and neck cancers. © 2016 Wiley Periodicals, *Head Neck* **39:** 56–62, 2017

KEY WORDS: cause-specific mortality, competing risks, cumulative incidence, prognosis, survival

INTRODUCTION

Reports of clinical trials on head and neck cancers contain a variety of primary endpoints, the most popular recently being "locoregional control," "overall survival," "local control," and "disease-free survival."[1] Also, "disease-specific" or "cause-specific" survival have been an often-used endpoint in trials but perhaps even more so in observational studies addressing the value of prognostic markers. Yet, from a patient's perspective, other endpoints than overall survival may be of limited interest. Overall survival depends on mortality from other causes of death, too, apart from that of the disease itself. Thus, the reality of competing risks deserves more attention than thus far mostly given in survival studies.[2] According to Mell et al,[2] estimating mortality from competing causes and evaluating the prognostic role of factors related to it would be useful in identifying treatment goals, tailoring individual cancer therapy, and selecting patients most likely to benefit from more intensive treatment.

Limited awareness seems to exist in the clinical community of the importance and pitfalls of competing risks analysis.[3] Quite often, competing causes of death are inadequately handled by presenting naïve Kaplan–Meier curves on "disease-specific survival,"[3,4] the aim being to assess the "net survival" (ie, probability of staying alive in a hypothetical scenario in which the only cause of death would be the cancer itself). Apart from problems in finding a meaningful interpretation to such curves in a real-life clinical setting, this naïve method treats deaths from competing causes as if they were random or noninformative censoring, the latter being a key condition for the validity of the Kaplan–Meier method. However, on reasonable grounds, this assumption can be questioned in most realistic instances.[3,4] A prime example about violation of random censoring is provided in the context of head and neck cancers, knowing that their major risk factors, tobacco and alcohol, are associated with several causes of death.

Appropriate statistical methods for competing risks analysis have been introduced in oncologic journals already 25 years ago,[5,6] and computational solutions have been available in major software environments, like R (R Foundation for Statistical Computing, Vienna, Austria),[4,7] SAS,[8] and Stata,[9] also over a decade. In recent years, examples of using these methods have started to appear in the clinical literature on the prognosis of patients with cancers of the head and neck.[2,10–14] Thus, positive methodological development has taken place, although typically in these reports the analyses remain somewhat incomplete with regard to recent recommendations[15] for fuller analysis of competing risks data. On the other hand, naïve Kaplan–Meier analysis of "disease-specific survival" seems, unfortunately, to prevail as the dominating approach with cause-specific mortality even in leading clinical journals.

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In this methodologically oriented communication, we illustrate how competing risk analysis is applied and what kind of insight it offers when describing and predicting cause-specific mortality in patients diagnosed with oral squamous cell carcinoma (OSCC), attempting to follow recent recommendations for analysis and reporting of such data.[15]

MATERIALS AND METHODS

Patient data

A population-based retrospective cohort design, including patients diagnosed with an OSCC between January 1, 1985 and December 31, 2005 from the 2 northernmost provinces of Finland, was used. The total population of the area is 738,000. Oulu University Hospital is the only tertiary referral center in the area.

The data were obtained from the files of the Finnish Cancer Registry and from the patients' records at Oulu University Hospital. The Finnish Cancer Registry receives notifications from practitioners and hospitals that are required to inform every new cancer diagnosed, and is considered to contain practically all malignancies diagnosed in the country since 1953.[16,17] All patients diagnosed during 1985 to 2005 with cancer of the oral cavity (codes C02-C06 in International Classification of Diseases, 10th revision) who were residents within the special responsibility area of Oulu University Hospital (covering the 2 northernmost provinces in Finland), were identified from the Cancer Registry. Eligible were patients whose cancer was histopathologically diagnosed as squamous cell carcinoma originating from the oral cavity. Thus, cancers of the lips, larynx, and pharynx were not included. The treatment of oral cancer was based primarily on the TNM classification. The treatment planning was done in a joint meeting with oncologists, head and neck surgeons, and plastic surgeons, and it followed the contemporary suggested guidelines.[18]

The hospital records of the patients were reviewed, and data on the following demographic and clinical items were gathered: sex, age at diagnosis, tumor size (T), and nodal involvement (N),[19] as well as comorbidity at diagnosis assessed by the Charlson's index.[20] We restricted the analysis to cover patients known to be M0 at diagnosis and for whom data on both T and N classification were also available. Follow-up information was obtained from the Finnish Cancer Registry, the records of which are annually matched through computerized linkage (based on personal identity codes), with the Cause of Death Register maintained by Statistics Finland, so that the dates and causes of death (also noncancerous causes, both underlying and contributory causes of death) are added to the records in the Registry. The Finnish Cancer Registry compares the official causes of death of each patient with cancer to all data available for that cancer, and makes a judgment whether the patient died of that cancer or something else. The classification of deaths into the 2 categories in this study: (1) deaths from OSCC; and (2) deaths of other causes, was based on that judgment. The records of the Finnish Cancer Registry are also regularly linked with the Central Population Register of Finland where the correctness of the personal identity codes is checked, and the complete name, vital status, possible date of death, or emigration, as well as the official place of residence before the date of diagnosis are obtained.[17] Follow-up of patients was started on the date of cancer diagnosis and ended on the date of death, migration, or the closing date of the follow-up, December 31, 2008.

This study was conducted in accordance with the ethical principles of the Helsinki Declaration and with the approval number STM/613/2005 of the Ministry of Social Affairs and Health of Finland, as well as the ethical committee of the University of Oulu and the Oulu University Hospital.

Statistical methods

Descriptive analyses of mortality from OSCC and from other causes, respectively, accounting for competing risks were performed by the well-known nonparametric estimator[4,21] of the pertinent cause-specific cumulative incidence function, this method being known as the Aalen–Johansen estimator in biostatistical literature.[22] Curves of the Aalen–Johansen estimates are presented together with those, known as 1–Kaplan–Meier curves,[9] that are based on the naïve Kaplan–Meier estimates of "cause-specific survival," in which the competing events are treated as if they were independent censorings.

After recent recommendations,[15] we applied 2 different regression approaches in parallel to analyze cause-specific mortality: (1) conventional Cox regression for cause-specific hazards; and (2) Fine–Gray model for subdistribution hazards. We first fitted Cox proportional hazards model on the cause-specific hazards of death (ie, cause-specific mortality rates) separately for the 2 outcomes: deaths from OSCC and from other causes, respectively.[15,22] In both models, age at diagnosis was included as a categorical covariate with 4 age bands. The following prognostic factors were also treated as categorical: sex (female vs male), tumor size (classes 2, 3, and 4, respectively, vs 1), nodal involvement (class 1, and combined class 2 and 3, both vs 0), and Charlson's comorbidity index (classes 1, and 2+, both vs 0). Based on the fitted Cox models for the cause-specific hazards of both competing causes of death, we then constructed predictions of cumulative incidence functions (ie, of cumulative probabilities of death both from OSCC and from other causes, respectively), by time since diagnosis for a few selected types of model patients representing different prognostic profiles. In this prediction, we applied a generalization of the Aalen–Johansen estimation adopted for Cox modeling of cause-specific hazards.[22]

As the second regression approach, we fitted a Cox-like regression model, known as the Fine–Gray model, for the subdistribution hazards of death from the 2 distinct causes.[15,22] The subdistribution hazard of dying from a given cause is a one-to-one mathematical transformation of the cumulative incidence function or risk of death for the same cause. A subdistribution hazard is different from the corresponding cause-specific hazard, and the subdistribution hazard ratios, (antilogarithms of the regression coefficients in a Fine–Gray model) do not have such a direct interpretation as the hazard ratios in a cause-specific hazard model.[15,22] However, prediction of cumulative probabilities of dying from a given cause of death is slightly more straightforward based on the Fine–Gray model, because the cumulative incidence function is directly obtained from the pertinent subdistribution hazard.

TABLE 1. Distributions of demographic and clinical characteristics of 306 patients with oral squamous cell carcinoma diagnosed during 1985 to 2005 in Northern Finland.

Characteristics	No. of patients (%)
Age, y	
15–49	56 (18)
50–64	101 (33)
65–74	80 (26)
75–93	69 (23)
Sex	
Men	167 (55)
Women	139 (45)
Charlson Comorbidity Index	
0	159 (52)
1	72 (24)
2	48 (16)
3–5	27 (9)
T classification	
T1	76 (25)
T2	124 (41)
T3	56 (18)
T4	50 (16)
N classification	
N0	211 (69)
N1	62 (20)
N2	29 (10)
N3	4 (1)

All the computations were performed using the R environment for statistical computing and graphics,[23] in particular, functions survfit and coxph in package survival, function Lexis in package Epi,[24] functions cuminc and crr in package cmprsk,[7] and functions CSC and predictEventProb in package risk Regression.[25]

RESULTS

A total of 339 patients met the initial eligibility criteria, of whom 306 (90%) were known to be M0 at diagnosis and for whom data on T and N classes were also available. The summaries of baseline characteristics are presented in Table 1. The median age of the patients was 65 years (range, 15–93 years), and 152 were female (45%). In more than one-third of the cases, the tumor size belonged to class T3 or T4, and in almost one-third, nodal involvement was present. About a half of the patients had some comorbidity according to the Charlson's index at the time of diagnosis.

Over one third ($n = 106$) of the patients were observed to die of their OSCC and somewhat less than that ($n = 94$) from other causes of death. The estimated cumulative incidence function curve showing cumulative mortality from OSCC (Figure 1A) has the characteristic pattern of a steep increase right after diagnosis and stabilization at the level of 35% by 10 years. No great difference exists between the Aalen–Johansen curve and the naïve 1-Kaplan–Meier curve. For other causes of death there is a steady increase in cumulative mortality over time exceeding 40% by 20 years since diagnosis, there being a bigger contrast developed between the 1-Kaplan–Meier and Aalen–Johansen estimates over time than for mortality from OSCC (Figure 1B).

Comparison of the estimated cumulative incidence functions for the 2 causes of death across different ages (see Figure 2) shows how the gap between the Aalen–Johansen estimates and the naïve 1-Kaplan–Meier estimates of cumulative incidence function is particularly wide for noncancer deaths in elderly patients. A disturbing feature of the naïve "cause-specific survival" curves in this age group is that the sum of the 1-Kaplan–Meier estimates for the cumulative mortalities of the 2 causes exceeds 100% already by 7 years since diagnosis. It is noteworthy that the clearly higher mortality from OSCC in this age group, as compared to those 50 to 64 years old (Figure 2A), is compensated in a nearly similar cumulative mortality from other causes in these 2 age groups (Figure 2B).

When modeling the cause-specific hazard and the subdistribution hazard of dying of OSCC both with the Cox model and with the Fine–Gray model, respectively, we found that age, large tumor size, and local spread of tumor were strongly predictive, but for nodal involvement the effect was weaker (Table 2). No discernible effects were observed for sex or Charlson's index when all the other factors considered were accounted for. The results of the Fine–Gray

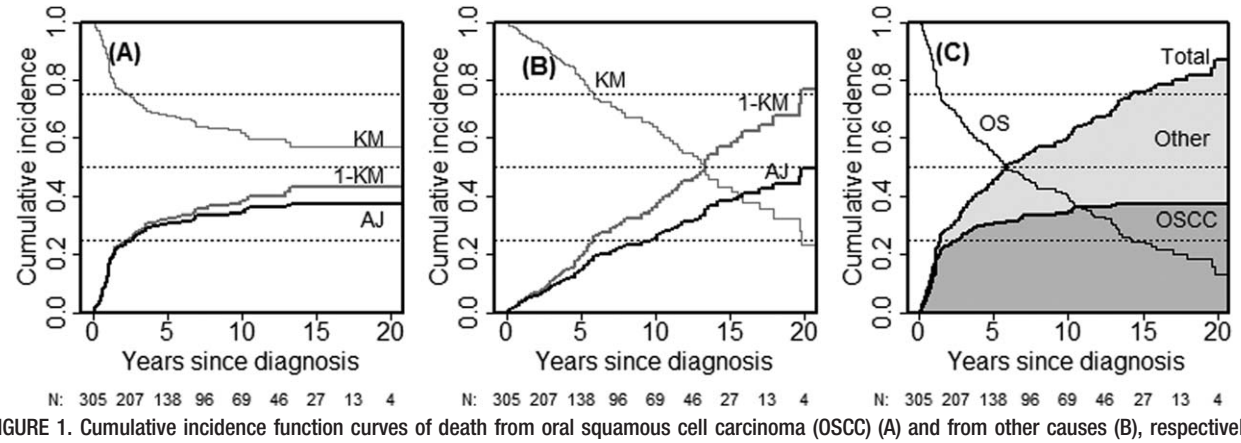

FIGURE 1. Cumulative incidence function curves of death from oral squamous cell carcinoma (OSCC) (A) and from other causes (B), respectively, accounting for the competing causes (Aalen–Johansen estimate [AJ]), or ignoring them (1-Kaplan–Meier [KM] estimate), and the corresponding naïve Kaplan–Meier curves of "cause-specific survival," as well as cumulative incidence function curves for the 2 causes of death stacked upon each other, and the overall survival (OS) curve (C). N = number of patients still at risk at selected times after diagnosis.

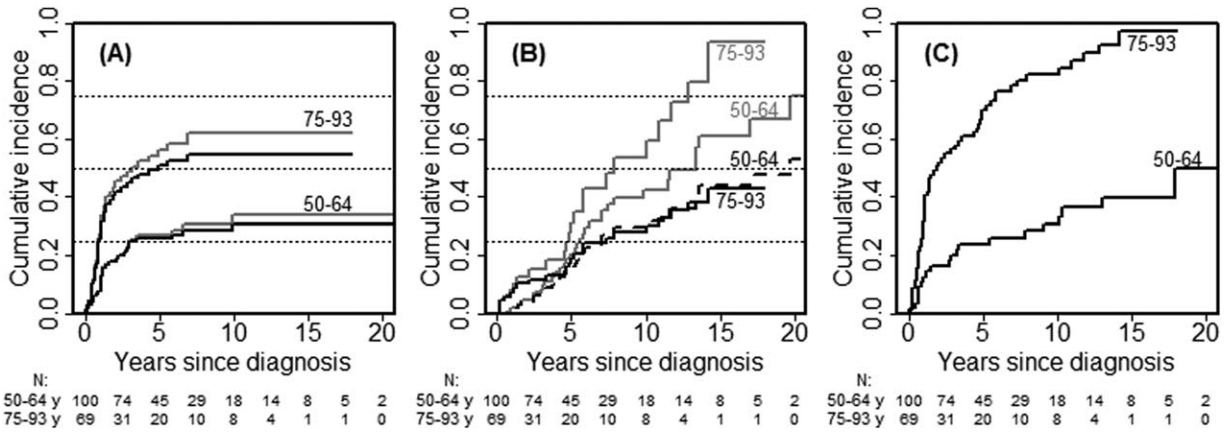

FIGURE 2. Cumulative incidence functions of death from oral squamous cell carcinoma (A), and from other causes of death (B), and for total mortality (C) in 2 age groups: 50 to 64 years, and 75 to 93 years, estimated by the Aalen–Johansen method (black lines, dashed for age group 50–64 years) and the naïve Kaplan–Meier method (gray lines). N = number of patients still at risk at selected times after diagnosis in the 2 age groups.

model for the subdistribution hazard of OSCC mortality were very similar.

The cause-specific hazard of dying of other causes was also positively associated with increasing age but less so than for OSCC deaths (Table 3). However, when modeling the subdistribution hazard, the estimated subdistribution hazard ratio for the age groups of 65 years and more indicated a nonelevated risk of death from these causes, as compared with age group 50 to 64 years. This pattern was different from that of the estimated cause-specific hazard ratios but it was consistent with the marginal cumulative incidence functions of Figure 2. According to both models, mortality from other causes was also dependent on sex and Charlson's index, whereas no evidence was found for nodal involvement having any effect on this component of mortality. High T class appeared to affect the cause-specific hazard but not the subdistribution hazard of deaths from other causes.

Based on the fitted Cox models for the 2 cause-specific hazards, we computed predicted probabilities of the relevant outcomes by time since diagnosis for various types of hypothetical patients representing different prognostic profiles. In Figure 3 are illustrated such predictions for 4 model patients ranging from one with relatively good prognosis (case A) to one with very poor prognosis (case D). Cases B and C have a remarkably similar prediction for total mortality, but the division of the latter into the 2 component causes is quite different, reflecting the contrasts in the patient profiles with respect to key tumor characteristics and major determinants of mortality from other causes. Analogous predictions were constructed based on the fitted Fine–Gray models on subdistribution hazards, and the results were very similar (data not shown), except for the model patient (case D) with the worst prognostic profile. In his case, the sum of the predicted cause-specific risks of death from the Fine–Gray model exceeded 100% before 15 years since diagnosis.

DISCUSSION

We used a population-based cohort of 306 patients with OSCC but without distant metastasis at baseline for demonstrating how to analyze the prognosis of these patients with the help of state-of-the-art statistical methods for dealing with competing risks.[3,15,21,22] Cumulative incidence functions were plotted for mortality from OSCC itself and from other causes, respectively, being estimated by the Aalen–Johansen method.[20,21] As recently recommended,[15] the impact of selected prognostic factors on both outcomes was analyzed using 2 approaches: conventional Cox regression was fitted for the cause-specific hazards, and the Fine–Gray model for the subdistribution hazards.[15,22] Finally, based on the fitted Cox models, individualized predictions on the risks of dying from the separate causes of death were computed for 4 types of model patients representing varying prognostic profiles. To our knowledge, this is the first time that such a comprehensive competing risks approach is applied in statistical analysis of cause-specific mortality of patients with OSCC.

From the patient's point of view, it is desirable to be informed about realistic estimates of the overall risks of death over time, not just because of cancer. For the clinician, it is important to have access to such population-based evidence on prognosis that is as all-encompassing as possible. Proper survival analysis by cause of death provides more detailed and clinically relevant prognostic insight upon simple analysis of overall survival. The novel approach advocated here provides realistic mortality predictions for various kinds of patients taking into account the key prognostic factors. As such, it offers a comprehensive prognosis, and can also serve as a tool in treatment planning. In particular, it overcomes the deficiency in curves showing "disease-specific survival," computed by naïve application of the Kaplan–Meier method. Such a curve attempts to describe survival experience in a fictitious world in which the patients would not die from other causes than their cancer and in which deaths from competing causes that actually occurred are questionably treated like noninformative censorings. This malpractice has been repeatedly criticized in a multitude of biostatistical references but also occasionally in oncologic journals already from the 1990s.[5,6,20,26]

TABLE 2. Cause-specific hazard ratios and subdistribution hazard ratios associated with selected prognostic factors, estimated from fitting a Cox model and a Fine–Gray model, respectively, on the mortality from oral squamous cell carcinoma, together with the pertinent 95% confidence intervals.

	Cox model		Fine–Gray model	
	Cause-specific hazard ratio	(95% CI)	Subdistribution hazard ratio	(95% CI)
Age at diagnosis (vs 50–64 y)				
15–49	0.68	(0.33–1.39)	0.74	(0.35–1.56)
65–74	1.30	(0.76–2.21)	1.28	(0.74–2.21)
75–93	2.73	(1.62–4.62)	2.46	(1.41–4.32)
Female sex	0.94	(0.62–1.40)	1.01	(0.66–1.53)
T classification (vs T1)				
T2	1.78	(0.94–3.39)	1.76	(0.95–3.26)
T3	2.81	(1.40–5.66)	2.58	(1.31–5.06)
T4	4.59	(2.29–9.19)	4.18	(2.06–8.47)
N classification (vs N0)				
N1	1.09	(0.67–1.79)	1.06	(0.64–1.77)
N2 or N3	2.02	(1.13–3.60)	1.84	(0.98–3.45)
Charlson Comorbidity Index (vs 0)				
1	0.82	(0.50–1.35)	0.78	(0.47–1.28)
2–6	1.33	(0.82–2.15)	1.02	(0.63–1.67)

Abbreviation: CI, confidence interval.

Cause-specific hazards and cumulative incidence functions are the quantities of clinical and statistical interest in the analysis of competing risks.[15] The cause-specific hazard ratios estimated from fitting a conventional Cox regression model on the cause-specific hazard of death from a given cause have a meaningful etiological interpretation. Assessment of the real-life risk of dying from a given cause, as estimated by the pertinent cumulative incidence function, is fundamentally based on the cause-specific hazards for all competing causes jointly. The alternative modeling approach based on the Fine–Gray model for the subdistribution hazards provides slightly more straightforward predictions for the risks of death by a given cause than that based on cause-specific hazards, also offering a possibility for constructing easy-to-use nomograms for risk prediction in a clinical setting.[11,14] On the other hand, the subdistribution hazard ratios do not have such a direct etiological interpretation as the cause-specific hazard ratios of the corresponding cause-specific hazard model. Yet, the cause-specific hazard ratio and subdistribution hazard ratio associated with the effect of a specific prognostic factor on the same outcome are related, but generally in a complicated manner.[26] Thus, the effect of a covariate on the subdistribution hazard (and consequently on cumulative incidence function) of a given cause can be different from its effect on the corresponding cause-specific hazard.

In our patient population, tumor size and nodal involvement had a clear effect on the mortality from OSCC. The risk of mortality increased with the tumor size and was clearly largest in cases in which the tumor had spread to adjacent structures. The effect of nodal involvement was

TABLE 3. Cause-specific hazard ratios and subdistribution hazard ratios associated with selected prognostic factors, estimated from fitting a Cox model and a Fine–Gray model, respectively, on the mortality from other causes of death, together with the pertinent 95% confidence intervals.

	Cox model		Fine–Gray model	
	Cause-specific hazard ratio	(95% CI)	Subdistribution hazard ratio	(95% CI)
Age at diagnosis (vs 50–64 y)				
15–49	0.38	(0.18–0.81)	0.49	(0.24–1.00)
65–74	0.99	(0.58–1.70)	0.94	(0.56–1.57)
75–93	1.75	(0.99–3.08)	0.95	(0.55–1.65)
Female sex	0.61	(0.40–0.95)	0.71	(0.46–1.09)
T classification (vs T1)				
T2	1.24	(0.71–2.17)	1.11	(0.65–1.90)
T3	1.24	(0.62–2.47)	1.03	(0.54–1.96)
T4	2.51	(1.18–5.34)	0.86	(0.41–1.80)
N classification (vs N0)				
N1	0.99	(0.57–1.70)	0.98	(0.58–1.67)
N2 or N3	1.44	(0.67–3.06)	0.85	(0.41–1.74)
Charlson Comorbidity Index (vs 0)				
1	1.02	(0.59–1.76)	1.23	(0.75–2.04)
2–6	3.53	(2.09–5.95)	2.05	(1.22–3.44)

Abbreviation: CI, confidence interval.

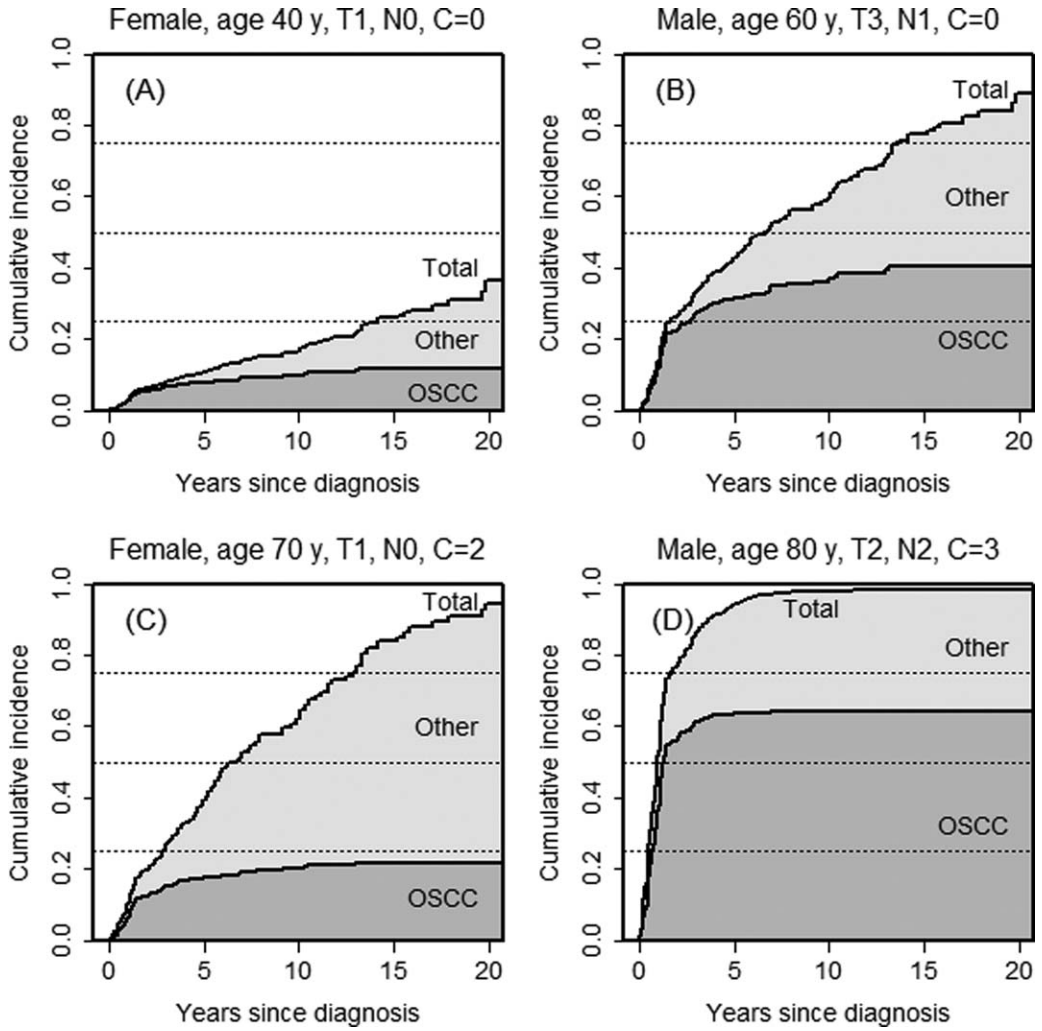

FIGURE 3. Predicted probabilities of dying from oral squamous cell carcinoma (OSCC; lower curve & darker gray area) and from other causes (light gray area between the 2 curves), and from all causes (total, the upper curve) by years since diagnosis for 4 kinds of model patients (T1, T2, and T3 refer to the tumor classification; N0, N1, and N2 to the nodal classification; and C to the value of Charlson's index, respectively, in these patients).

more modest even to the extent that metastasis in a single small ipsilateral lymph node did not increase the mortality risk significantly. Only metastasis in larger or multiple ipsilateral, contralateral, or bilateral lymph nodes increased the mortality risk moderately. Sex and Charlson's comorbidity index were associated with an elevated mortality from other causes in both modeling approaches. These similarities were actually what one would expect based on both mathematical arguments and empirical experience.[3,15,26,27] With regard to the age at diagnosis, we found somewhat discrepant results in our models concerning the mortality from other causes of death, especially for more senior patients ($\geq$65 years). This apparent paradox is explained by the fact that the subdistribution hazard ratio reflects only partly the effect of the factor of interest on the pertinent cause-specific hazard, but is also essentially influenced by the effect of this factor on the other component of mortality. Other scenarios concerning cause-specific hazard ratios and subdistribution hazard ratios and their mutual dependency in various circumstances are illustrated by Dignam et al.[26]

One important shortcoming of the Fine–Gray model is that, in some cases, the sum of the predicted risks of death from the separate causes of death based on individual subdistribution hazards may exceed 100%, this anomaly being actually realized in one of our model patients. Such a disturbing feature is never encountered when risk predictions are based on all cause-specific hazards, because of the coherent mathematical representation of each separate cumulative incidence functions in terms of all cause-specific hazards. Finally, the approach based on subdistribution hazards would not be applicable in a more general multistate setting,[4,28] which, in addition to deaths from alternative causes, may contain the possibility of relevant intermediate states in the postdiagnosis course of disease, like local or regional recurrences. In such a setting, the basic building blocks are transition-specific hazards,[28] including hazards of recurrence and cause-specific hazards of death, the latter either without or with passing via the state of recurrence.

Our empirical data had a few shortcomings. First, the patient population was quite small in comparison with

studies comprising representative material from thousands of subjects.[10,14] Second, only a very limited set of prognostic factors were available. In many previous reports applying competing risks analysis,[2,10–14] more detailed information on relevant baseline characteristics were utilized. Smoking, in particular, would be an important predictor of mortality for both causes of death. Unfortunately, the clinical records available to us contained only very deficient data on the smoking history of the patients. Because of this, it was reasonable not to include smoking in this modeling exercise, which obviously limits the generalizability of our empirical results. As to assignment of the cause of death, we relied on the judgment made by the Finnish Cancer Registry; primarily based on the official death certificate but taking also into account the recorded cancer history of the patient. This judgment, although not perfect, is probably no more ambiguous than any other cause of death assignment. We could also have applied more refined modeling in our analysis (for example, treating age at diagnosis as a continuous covariate and suitable smoothing splines[29] applied to describe its effect and including relevant time by covariate interaction terms for a possibly better fit of the cause-specific hazard model for OSCC deaths in particular). We omitted these complications in the interest of keeping this tutorial presentation concise and focused on the main principles of competing risks analysis.

Previous studies[2,10–14] addressing competing outcomes in patients with head and neck cancer have typically limited their analytic effort to modeling only subdistribution hazard but not cause-specific hazard, and predicting cumulative incidence functions based on the fitted subdistribution hazard model. In comparison to them, the main strength of our study was that we conducted a full analysis, including descriptive plots of cumulative incidence functions, fitting cause-specific hazards by Cox regression, as well as subdistribution hazards by the Fine–Gray model for both causes of death, and computing predictions for risks of death by time since diagnosis for patients with various prognostic profiles. Such many-sided analysis has recently been recommended[15] for competing risks data, because it provides much more detailed information and deeper insight on the prognostic problem than analyses applying only Fine–Gray modeling and conducted and reported for only one outcome.

A natural next step to enrich our analysis would be a more comprehensive assessment of the prognosis of patients with cancer, which requires inclusion of the possibility of local and regional recurrences and the impact of them on the subsequent survival scenarios. Also, it is desirable to be able to compute updated prognostic probabilities for a patient, who has already survived, such as 1 year or 5 years, also conditional on whether and when a recurrence has taken place. Multistate models[4,28] have previously been applied to such comprehensive assessment of prognosis, at least for patients with breast cancer.[30,31]

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