**Competing risks analysis of cause-specific mortality in patients with oral squamous cell carcinoma** (Final draft)

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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 post-diagnosis 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 analysed 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 description and prediction 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 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.

## INTRODUCTION

Reports of clinical trials on head and neck cancers contain a variety of primary endpoints, the most popular recently being "loco-regional control", "overall survival", "local control", and "disease-free survival".[1] Also, "disease-specific" or "cause-specific" survival has 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 of mortality from other causes of death, too, apart from that from the disease itself. The reality of *competing risks* deserves thus more attention than thus far mostly given in survival studies.[2] According to Mell *et al*., 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.[2]

Limited awareness appears to exist in the clinical community of the importance and pitfalls of competing risks analysis.[4] Quite often competing causes of death are inadequately handled by presenting naïve Kaplan-Meier curves on "disease-specific survival",[4,5] the aim being to assess the "net survival", i.e. 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 non-informative censoring, the latter being a key condition for the validity of the Kaplan-Meier method. However, this assumption can on reasonable grounds be questioned in most realistic instances.[4,5] 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 oncological journals already 25 years ago,[6,7] and computational solutions have been available in major software environments like R,[5,8] SAS,[9] and Stata[10] 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 head and neck.[2,3,11,12,13,14] Positive methodological development has thus 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.

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 two northernmost

provinces of Finland, was used. The total population of the area is 738 000. Oulu University Hospital is the only tertiary referral centre in the area.

The data were obtained from the files of the Finnish Cancer Registry and from the patient 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 oral cavity (codes C02-C06 in ICD-10, International Classification of Diseases, 10th revision) resident within the special responsibility area of Oulu University Hospital (covering the two northernmost provinces in Finland), were identified from the Cancer Registry. Eligible were patients whose cancer was histo-pathologically diagnosed as squamous cell carcinoma originating from oral cavity (OSCC). Cancers of lip, larynx and pharynx were thus not included. The treatment of oral cancer was based primary on the TNM stage. The treatment planning was done in a joint meeting with oncologists, head and neck 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, tumour size T, and nodal involvement N,[19] as well as co-morbidity 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 class were also available. Follow-up information was obtained from the Finnish Cancer Registry, the records of which are annually matched, through computerised linkage (based on personal identity codes, PIC), with the Cause of Death Register maintained by Statistics Finland, so that the dates and causes of death (also non-cancerous 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 cancer patient to all data available for that cancer, and makes a judgment whether the patient died from that cancer or something else. The classification of deaths into the two categories in this study: deaths from OSCC and deaths from 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 PICs is checked, and the complete name, vital status, possible date of death or emigration as well as the official place of residence prior to 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 no. STM/613/2005 of the Ministry of Social Affairsand 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 non-parametric estimator[5,21] of the pertinent cause-specific *cumulative incidence function* (CIF), this method being known as *Aalen-Johansen estimator* (AJ) in biostatistical literature.[22] Curves of AJ estimates are presented together with those, known as 1–KM curves[10], that are based on the naïve Kaplan-Meier (KM) estimates of "cause-specific survival", in which the competing events are treated as if they were independent censorings.

Following recent recommendations[15] we applied in parallel two different regression approaches to analyse 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* (CSH) of death, i.e. cause-specific mortality rates, separately for the two outcomes: deaths from OSCC and from other causes, respectively.[15,22] In both models age at diagnosis was included as a categorical covariate with four age bands. The following prognostic factors were also treated as categorical: sex (female vs. male), tumour size T (classes 2, 3 and 4, respectively, vs. 1), nodal involvement N ( class 1, and combined class 2&3, both vs. 0), and Charlson's comorbidity index (classes 1, and 2+, both vs. 0)Based on the fitted Cox models for the CSHs of both competing causes of death, we then constructed predictions of CIFs, i.e. 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 modelling of CSHs[22].

As the second regression approach we fitted a Cox like regression model, known as the *Fine-Gray model*, for the *subdistribution hazards* (SDH) of death from the two distinct causes.[15,22] The SDH of dying from a given cause is a one-to-one mathematical transformation of the CIF or risk of death for the same cause. A SDH is different from the corresponding CSH, and the subdistribution hazard ratios (SDHR), (antilogarithms of the regression coefficients in a Fine-Gray model) do not have such a direct interpretation as the hazard ratios in a CSH 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 CIF is directly obtained from the pertinent SDH

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,[8] and functions CSC and predictEventProb in package riskRegression.[25]

## RESULTS

[TABLE 1 ABOUT HERE]

A total of 339 patients met the initial eligibility criteria, out 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 (range 15-93) years, and 152 (45%) were female. In more than one third of the cases the tumour 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.

[FIGURE 1 ABOUT HERE]

Over one third (n=106) of the patients were observed to die from their OSCC and somewhat less than that (n=94) from other causes of death. The estimated CIF curve showing cumulative mortality from OSCC (Figure 1 (A)) has the characteristic pattern of steep increase right after diagnosis and stabilization at the level of 35% by 10 years. No great difference exists between the Aalen-Johansen (AJ) curve and the naïve one minus Kaplan-Meier (1−KM) 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−KM and AJ estimates over time than for mortality from OSCC (Figure 2(B)).

[FIGURE 2 ABOUT HERE]

Comparison of the estimated CIFs for the two causes of death across different ages (Figure 2) shows how the gap between the AJ estimates and the naïve 1−KM estimates of CIF is particularly wide for non-cancer 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−KM estimates for the cumulative mortalities of the two 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 2 (A)) is compensated in a nearly similar cumulative mortality from other causes in these two age groups (Figure 2 (B)).

[TABLE 2 ABOUT HERE]

When modelling the cause-specific hazard (CSH) and the sub-distribution hazard (SDH) of dying from OSCC both with the Cox model and with the Fine-Gray model, respectively, we found that age, large tumour size and local spread of tumour were strongly predictive, but for nodal involvement the effect was weaker (Table 2). No discernible effects were observed for gender or Charlson's index when all the other factors considered were accounted for. The results of the Fine-Gray model for the SDH of OSCC mortality were very similar.

[TABLE 3 ABOUT HERE]

The CSH of dying from other causes was also positively associated with increasing age but less so than for OSCC deaths (Table 3). However, when modelling the sub-distribution hazard the estimated SDHR for the age groups of 65 years and more

indicated a non-elevated risk of death from these causes as compared with age group 50 to 64 years. This pattern was different from that of the estimated CSHRs but it was consistent with the marginal CIFs of Figure 2. According to both models, mortality from other causes was also dependent on gender 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 CSH but not the SDH of deaths from other causes.

[FIGURE 3 ABOUT HERE]

Based on the fitted Cox models for the two CSHs 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 four model patients ranging from one with relatively good prognosis (case A) to one with very poor prognosis (D). Cases B and C have a remarkably similar prediction for total mortality, but the division of the latter into the two component causes is quite different, reflecting the contrasts in the patient profiles with respect to key tumour characteristics and major determinants of mortality from other causes. Analogous predictions were constructed based on the fitted Fine-Gray models on SDHs, and the results were very similar (data not shown), except for the model patient (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 oral squamous cell carcinoma (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.[4,15,21,22] Cumulative incidence functions (CIF) were plotted for mortality from OSCC itself and from other causes, respectively, being estimated by the Aalen-Johansen (AJ) method.[20,21] As recently recommended[15] the impact of selected prognostic factors on both outcomes was analyzed using two approaches: conventional Cox regression was fitted for the cause-specific hazards (CSH), and the Fine-Gray model for the sub-distribution hazards (SDH)[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 four types of model patients representing varying prognostic profiles. To our knowledge this is the first time that such a comprehensive competing risks approachis applied in statistical analysis of cause-specific mortality of patients with oral squamous cell carcinoma.

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 due to 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 (KM) method. Such a curve attempts to describe survival experience in a fictitious world where 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 non-informative censorings. This malpractice has been repeatedly criticized in a multitude of biostatistical references but also occasionally in oncological journals already from the 1990s.[6,7,20,26]

CSHs and CIFs are the quantities of clinical and statistical interest in the analysis of competing risks.[15] The cause-specific hazard ratios (CSHR) estimated from fitting a conventional Cox regression model on the CSH 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 CIF, is fundamentally based on the CSHs for all competing causes jointly. The alternative modelling approach based on the Fine-Gray model for the subdistribution hazards (SDH) provides slightly more straightforward predictions for the risks of death by a given cause than that based on CSHs, also offering a possibility for constructing easy-to-use nomograms for risk prediction in a clinical setting.[11,14] On the other hand, the sub-distribution hazard ratios (SDHR) do not have such a direct etiological interpretation as the CSHRs of the corresponding CSH model. Yet, the CSHR and SDHR 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 SDH (and consequently on CIF) of a given cause can be different from its effect on the corresponding CSH.

In our patient population tumour 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 where tumor had spread to adjacent structures. The effect of nodal involvement was 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. Gender and Charlson’s comorbidity index

were associated with an elevated mortality from other causes in both modelling approaches. These similarities were actually what one would expect based on both mathematical arguments and empirical experience.[4,15,26,27] With regard to the age at diagnosis we found somewhat discrepant results in our modelsconcerning the mortality from other causes of death, especially for more senior patients (≥ 65 y). . This apparent paradox is explained by the fact that the SDHR reflects only partly the effect of the factor of interest on the pertinent CSH, but is also essentially influenced by the effect of this factor on the other component of mortality. Other scenarios concerning CSHRs and SDHRs 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 SDHs 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 CSHs, because of the coherent mathematical representation of each separate CIFs in terms of all CSHs. Finally, the approach based on SDHs would not be applicable in a more general multi-state setting,[5,28] which in addition to deaths from alternative causes may contain the possibility of relevant intermediate states in the post-diagnosis 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 CSHs 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.[3,14] Second, only a very limited set of prognostic factors were available. In

many previous reports applying competing risks analysis[2,3,11,12,13,14] 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 modelling 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 modelling 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 CSH 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[2,3,11,12,13,14] addressing competing outcomes in patients head and neck cancer patients have typically limited their analytic effort to modelling only SDH but not CSH, and predicting CIFs based on the fitted SDH model. In comparison to them, the main strength of our study was that we conducted a full analysis including descriptive plots of CIFs, fitting CSHs by Cox regression as well as SDHs 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 modelling 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 cancer patients, 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, say, one year or five years, also conditional on whether and when a recurrence has taken place. Multi-state models[5,28] have previously been applied to such comprehensive assessment of prognosis at least for patients with breast cancer.[30,31]

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## LIST OF TABLES

## FIGURE LEGENDS

**FIGURE 1.** Cumulative incidence function (CIF) curves of death from oral squamous cell carcinoma (panel A) and from other causes (panel B), respectively, accounting for the competing causes (AJ, Aalen-Johansen estimate), or ignoring them (1−KM estimate), and the corresponding naïve Kaplan-Meier (KM) curves of "cause-specific survival", as well as CIF curves for the two causes of death stacked upon each other, and the overall survival (OS) curve (panel C). N = no. of patients still at risk at selected times after diagnosis.

**FIGURE 2.** Cumulative incidence functions of death from oral squamous cell carcinoma (panel A), and from other causes of death (panel B), and for total mortality (panel C) in two age groups: 50-64 y, and 75-93 y, estimated by the Aalen-Johansen method (black lines, dashed for age group 50-64 y) and the naïve Kaplan-Meier method (gray lines). N = no. of patients still at risk at selected times after diagnosis in the two age groups.

**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 two curves), and from all causes (Total, the upper curve) by years since diagnosis for four kinds of model patients (T1, T2, and T3 refer to the T class; N0, N1, and N2 to the N class; and C to the value of Charlson's index, respectively, in these patients).

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

| | No. of patients (%) |
|---|---|
| Age (years) | |
| 15-49 | 56 (18) |
| 50-64 | 101 (33) |
| 65-74 | 80 (26) |
| 75-93 | 69 (23) |
| Gender | |
| Men | 167 (55) |
| Women | 139 (45) |
| Charlson's 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) |

**TABLE 2.** Cause-specific hazard ratios and sub-distribution 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.

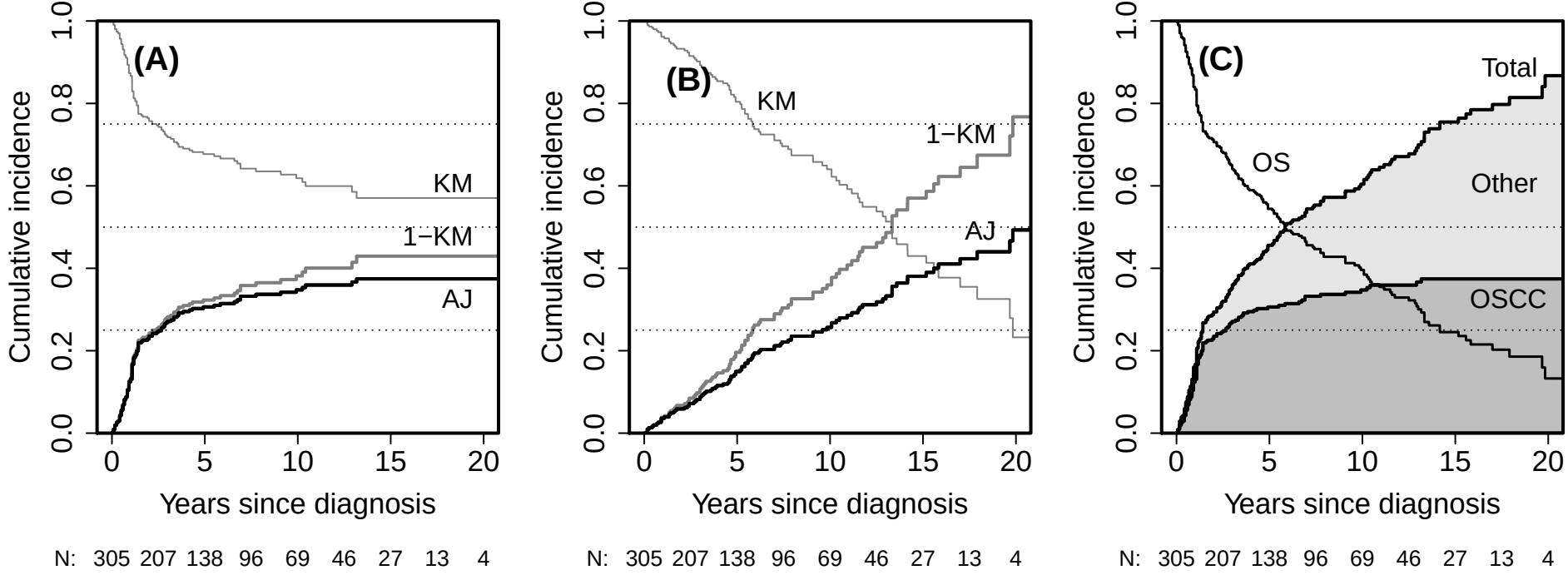
| | Cox model | | Fine-Gray model | |
|---|---|---|---|---|
| | CSHR | 95% CI | SDHR | 95% CI |
| Age at diagnosis (vs. 50-64 y) | | | | |
| 15-49 | 0.68 | (0.33 − 1.39) | 0.74 | (0.35 – 1.56) |
| 65-74 | 1.30 | (0.76 – 2.21) | 1.28 | (0.74 – 2.21) |
| 75-93 | 2.73 | (1.62 – 4.62) | 2.46 | (1.41 – 4.32) |
| Female gender | 0.94 | (0.62 − 1.40) | 1.01 | (0.66 − 1.53) |
| Tumour size (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) |
| Nodal involvement (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’s 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) |

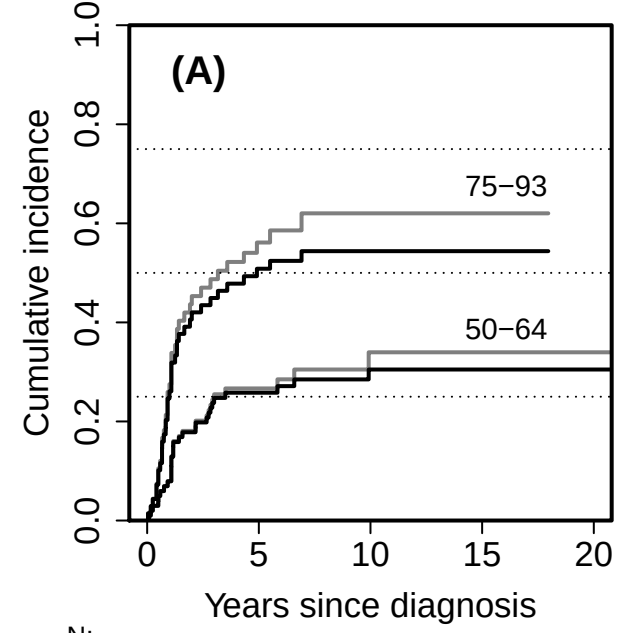
Abbreviations: CSHR, cause-specific hazard ratio; SDHR, sub-distribution hazard ratio; CI, confidence interval.

**TABLE 3.** Cause-specific hazard ratios and sub-distribution 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 | |
|---|---|---|---|---|
| | CSHR | 95% CI | SDHR | 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 gender | 0.61 | (0.40 – 0.95) | 0.71 | (0.46 - 1.09) |
| Tumour size (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) |
| Nodal involvement (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’s 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) |

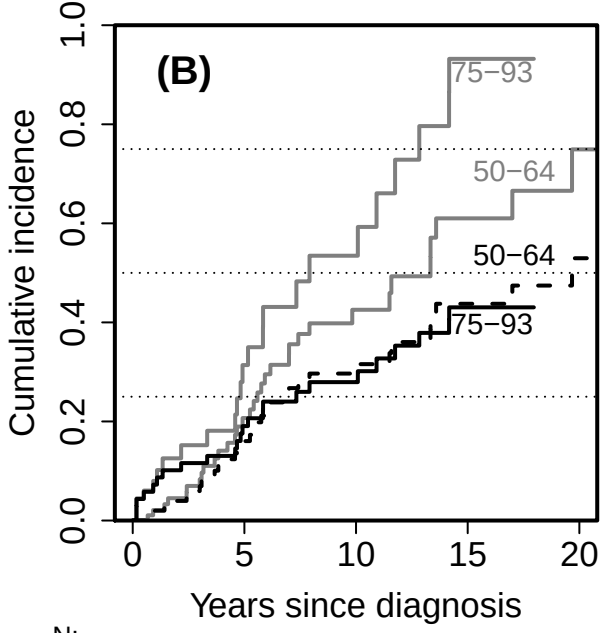
Abbreviations: CSHR, cause-specific hazard ratio; SDHR, sub-distribution hazard ratio; CI, confidence interval.


(A)
KM
1−KM
AJ
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
Years since diagnosis
N: 305 207 138 96 69 46 27 13 4
(B)
KM
1−KM
AJ
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
Years since diagnosis
N: 305 207 138 96 69 46 27 13 4
(C)
Total
OS
Other
OSCC
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
Years since diagnosis
N: 305 207 138 96 69 46 27 13 4



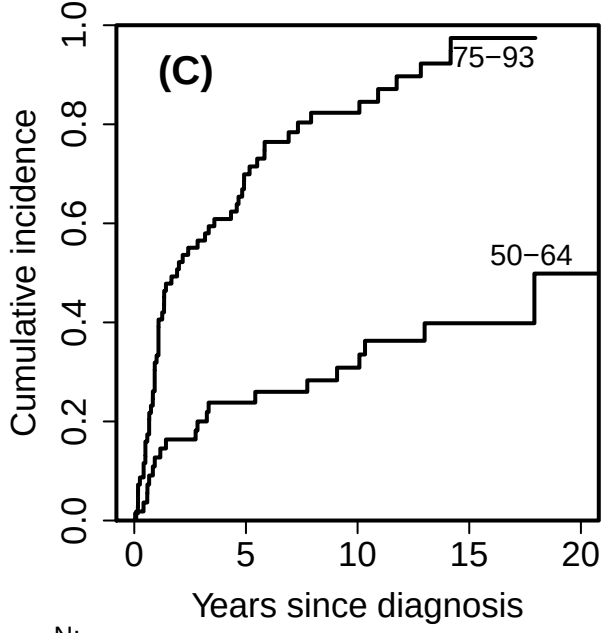

N:

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 50−64 y | 100 | 74 | 45 | 29 | 18 | 14 | 8 | 5 | 2 |
| 75−93 y | 69 | 31 | 20 | 10 | 8 | 4 | 1 | 1 | 0 |



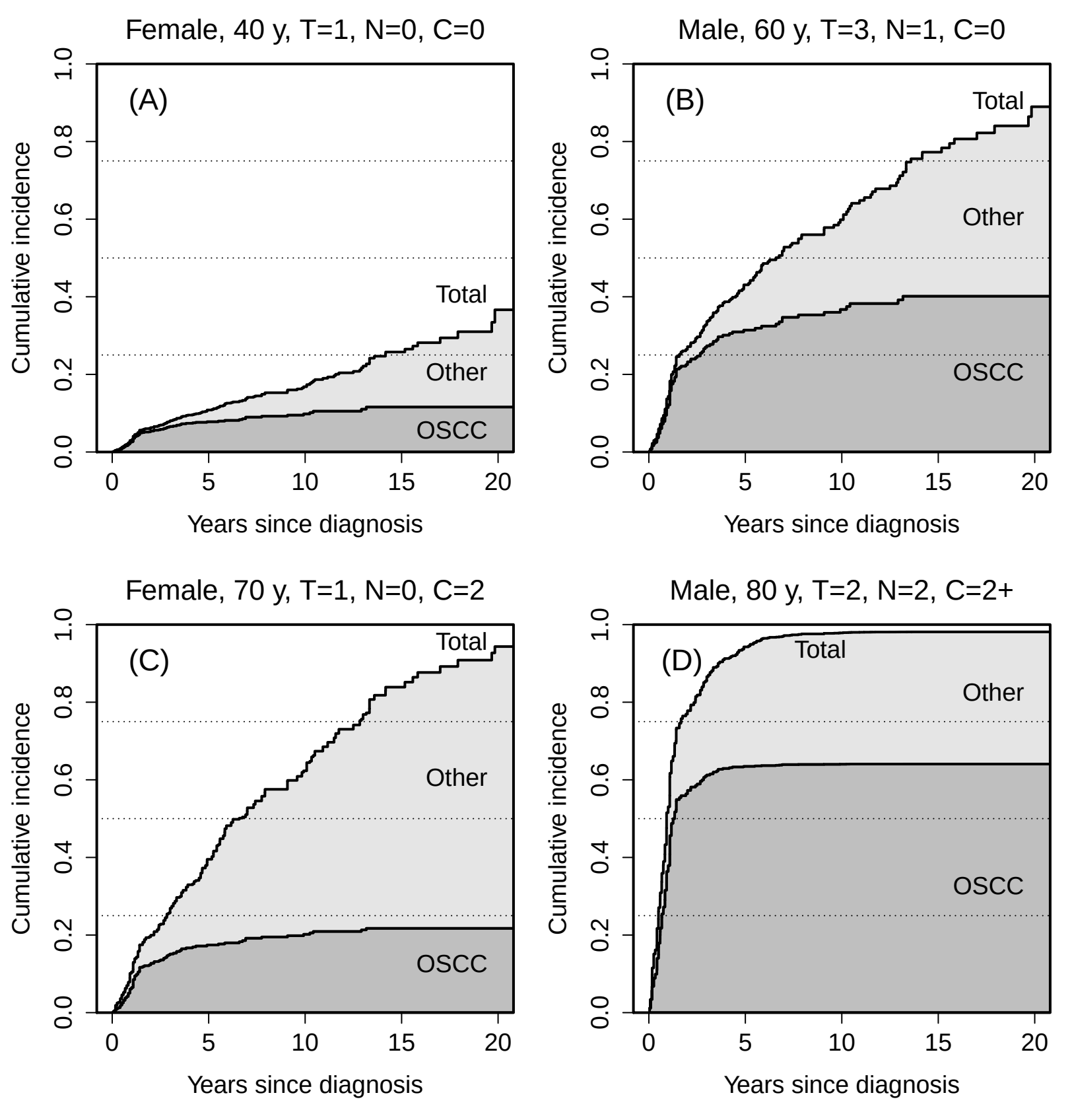

N:

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 50−64 y | 100 | 74 | 45 | 29 | 18 | 14 | 8 | 5 | 2 |
| 75−93 y | 69 | 31 | 20 | 10 | 8 | 4 | 1 | 1 | 0 |




N:

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 50−64 y | 100 | 74 | 45 | 29 | 18 | 14 | 8 | 5 | 2 |
| 75−93 y | 69 | 31 | 20 | 10 | 8 | 4 | 1 | 1 | 0 |


Female, 40 y, T=1, N=0, C=0
(A)
Total
Other
OSCC
Male, 60 y, T=3, N=1, C=0
(B)
Total
Other
OSCC
Female, 70 y, T=1, N=0, C=2
(C)
Total
Other
OSCC
Male, 80 y, T=2, N=2, C=2+
(D)
Total
Other
OSCC
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
Years since diagnosis