

**Impact of local recurrence on cause-specific
death after stereotactic body radiotherapy for
early-stage non-small cell lung cancer:
dynamic prediction using landmark model**

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**Impact of local recurrence on cause-specific death after stereotactic body
radiotherapy for early-stage non-small cell lung cancer: dynamic prediction using
landmark model**

Short running title

Impact of LR on CSD after SBRT for ES-NSCLC

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Conflict of interest

Dr Matsuo reported receiving grants from Varian Medical Systems outside the submitted work as well as payment for lectures from AstraZeneca outside the submitted work. Dr Takeda reported receiving grants from Varian Medical Systems outside submitted work as well as consulting fees from Accuray Japan K.K. outside submitted work. Dr Mizowaki reported receiving grants from Varian Medical Systems outside submitted work as well as consulting fees from Hitachi outside submitted work.

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Abstract

Purpose. The purpose of this study was to assess the impact of local recurrence (LR) on cause-specific death (CSD) in patients with non-small cell lung cancer (NSCLC) treated with stereotactic body radiotherapy (SBRT). A dynamic prediction model that incorporated LR as a time-dependent covariate was used.

Methods and materials. This study included 535 stage I (cT1–T2aN0M0) NSCLC patients treated with SBRT from two institutions. We developed a landmark dynamic prediction model to estimate the probability of a CSD. This model determined the probability of surviving for an additional 3 years at different prediction time points during follow-up, given the history of recurrence status. The baseline covariates included in the model were age, sex, T stage, and histology, while the time-dependent covariates were LR and regional and/or distant recurrence (RDR) status.

Results. Overall, 137 patients (25.6%) died of lung cancer within a median follow-up of 4.1 years. Of the 195 patients who developed recurrence, 28, 125, and 42 patients had LR only, RDR only, and both, respectively. The landmark model showed that older age, advanced T stage, LR, and RDR were significantly associated with an increased risk of subsequent CSD. Among these covariates, LR (odds ratio [OR], 8.5; 95% confidence interval [CI], 6.0–12.0; $P < .001$) and RDR (OR, 11.6; 95% CI, 9.1–14.9; $P < .001$) demonstrated strong effects on CSD within 3 years after the prediction time points. The dynamic prediction provided information on the probability of future CSD according to individual recurrence status during follow-up.

Conclusions. Dynamic prediction using the landmark model showed that LR had a substantial impact on subsequent CSD, which was comparable to that of RDR. This result supports the notion that strategies to improve local control are reasonable.

Introduction

Stereotactic body radiotherapy (SBRT) is the standard treatment for patients with medically inoperable early-stage non-small cell lung cancer (ES-NSCLC) (1). Although a biologically effective dose (BED) of 100 Gy is generally accepted as the standard dose required to obtain a high local control rate (2,3), regimens exceeding BED of 100 Gy to achieve higher local control have also been investigated. Phase II clinical trials that used high BED demonstrated a high local control rate of 98% at 3 years (4) and 96% at 2 years (5). However, the impact of improved local control on survival remains unclear owing to limited randomized data comparing between higher and standard doses. Several retrospective studies and meta-analyses that compared between standard and high doses have shown that higher doses benefit local control (3,6-10). However, these studies yielded conflicting results regarding whether improved local control leads to improved overall survival (OS). Therefore, we attempted to consider this clinical question in an alternative way, specifically by directly inferring a causal relationship between local recurrence (LR) and survival.

This causal inference cannot be analyzed with standard “static” approaches such as the Cox model or the Fine-Gray model that start an analysis from time zero (e.g., X-year survival rate) because the recurrence status is a dynamic variable that is measured during follow-up and whose values change dynamically over time. To incorporate such dynamic variables into a prediction model, van Houwelingen introduced dynamic prediction using the landmark model, which is robust against misspecification of the proportional hazards assumption (11).

The purpose of this study was to investigate, using the landmark dynamic prediction model, the extent to which LR occurring at a specific time point during follow-up increased subsequent cause-specific death (CSD) in patients with ES-NSCLC treated with SBRT.

Methods and Materials

Patient population

This study included 535 patients who underwent SBRT for clinical stage I (T1–2aN0M0, the American Joint Committee on Cancer 8th edition) primary NSCLC between 2003 and 2014 at Kyoto University Hospital (KUH) and between 2005 and 2015 at Ofuna Chuo Hospital (OCH) (Table 1). The exclusion criteria were an Eastern Cooperative Oncology Group performance status of 3–4, SBRT for palliative purposes or with maximum doses of BED < 100 Gy, and SBRT with ≥ 9 fractions.

At staging, patients underwent computed tomography (CT) and ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET). NSCLC pathology was proven, except in patients that were unable to undergo biopsy procedures for clinical or technical reasons or patients examined but without confirmation of pathological status. In such patients, the diagnosis of primary NSCLC was determined by the lung cancer board based on the clinical information including CT findings, serial enlargement on CT images, increased standardized maximum uptake value of ^{18}F -FDG-PET/CT, and increased tumor markers. We calculated the BED using a linear quadratic model at an alpha-beta ratio of 10 Gy.

This study was approved by the institutional review board of each institution. The requirement for informed consent was waived owing to the retrospective nature of the study.

SBRT protocol

The details of SBRT procedures in each institution have been described in previous reports (12-15). In KUH, we delivered 48 Gy in 4 fractions to the isocenter for peripheral tumors and 60 Gy in 8 fractions to the isocenter for central tumors, which represent BED at the isocenter of 105.6 Gy and 105 Gy, respectively. Since 2006, the dose was increased to 56 Gy in four fractions for a peripheral tumor with a diameter > 30 mm, which is equivalent to a BED of 134.4 Gy at the isocenter. In OCH, we prescribed 40–60 Gy in 5 fractions to the 60%–80% isodose line of the maximal dose covering the planning target volume (PTV), depending on the location of tumors. These are equivalent to a BED of 100–300 Gy at the maximal dose in PTV.

Follow-up and event definitions

Follow-up CT intervals were generally the same at both institutions. Patients were followed up at 1–4 months, at 3–6 months, every 3-6 months until the 5th year, and then annually thereafter. Recurrences were classified as local (within or adjacent to the PTV), regional (hilar, mediastinal, or supraclavicular fossa), or distant (any other sites). LR was diagnosed based on histopathological confirmation or imaging findings as follows: an increase in cross-sectional tumor size greater than 25% on at least three consecutive CT scans over 6 months, an increase in size that was not attributable to pulmonary fibrosis, or increased standard uptake values of ^{18}F -FDG-PET at the site of suspected LR. If the diagnosis of LR was difficult, the diagnosis was made by the tumor board. If patients were suspected of having disease progression other than LR, we performed ^{18}F -FDG-PET and/or magnetic resonance imaging of the brain in addition to CT. The differential diagnosis of pulmonary metastasis from second primary lung cancer (SPLC) was based on the American College of Chest Physicians practical guidelines (16). In complex cases

in which SPLC was difficult to distinguish from pulmonary metastasis, the diagnosis was made by the tumor board. CSD was defined as death due to primary NSCLC, accounting for non-specific death from other causes (NSD) as a competing terminal event. NSD included deaths from fatal adverse events associated with SBRT, deaths from other malignancies, deaths from SPLC, and deaths from unknown causes without evidence of recurrence. The time to event was calculated from the start date of SBRT to the date of the event.

Statistical analysis

OS was estimated using the Kaplan–Meier method. The rates of LR, non-local recurrence (i.e., regional and/or distant recurrence [RDR]), CSD, and NSD were estimated using the cumulative incidence function. For LR and RDR, both CSD and NSD were considered as competing risks. To assess the effect of recurrence on the cumulative incidence of CSD, landmark analysis was performed using the pseudo-value regression model (17). CSD, rather than OS, was selected as the outcome measure for estimating the effect of recurrence on CSD because the causal relationship between cancer recurrence and NSD is likely to be much weaker than that between recurrence and CSD. The concept of landmarking updates survival probabilities during follow-up, given the history of recurrence status and baseline information by selecting only the patients who are alive and at risk (11). Age, sex, T stage, and histology were included as the baseline variables. The selection of these baseline variables was based on clinical knowledge of and previous literature on the risk factors for CSD after SBRT in ES-NSCLC (12,15,18). LR and RDR are binary time-dependent variables experienced by at-risk patients up to the prediction time points. Since, by definition, a diagnosis of LR required at least 6 months of follow-up, the landmark time point started at 1 year after SBRT. The last landmark time point was set

at 4 years because the at-risk patients decreased after 4 years of SBRT. Considering our follow-up interval of 3-6 months, a grid of 13 landmark time points every third month between 1 and 4 years after SBRT was created. The prediction interval width (window) was fixed at 3 years, that is, a prognosis within 3 years was predicted from each landmark time point. The setting of this window was arbitrary, though we also referred to the literature on survival rates after LR (19). We considered the landmark "supermodel" in which we expected regression coefficients to vary smoothly with time (11). Specifically, the "separate" models at 13 different landmark time points were combined into a single model. This single model provides the cumulative incidence of CSD within 3 years for any prediction time point (hereinafter called 3-year dynamic CSD). This supermodel considered linear associations with landmark time. The main covariates and linear term of landmark time were included in the model, irrespective of the statistical significance. Pseudo-values for patients at risk were defined and used to replace the event indicators among all patients, including censored patients. The landmark model was fitted on the pseudo-values with covariates using generalized estimating equations, which was an extension of the generalized linear regression. All statistical analyses were performed using R software (version 3.6.3, www.r-project.org). Differences were considered statistically significant at a p-value of 0.05.

Results

Overview of outcomes

Within a median follow-up of 4.1 (interquartile range [IQR], 2.2–6.2) years, 326 patients (62.8%) died; of them, 137 patients died of primary NSCLC (i.e., CSD), and 199 died of other causes (i.e., NSD). As shown in Figure 1A, the incidence of new CSD

decreased around the fourth year, while that of NSD continued to increase with time after SBRT. As for recurrence, most LRs (85.7%) occurred within the first 4 years after SBRT (Fig. 1B). Meanwhile, the incidence of new RDR continued to increase even at 4 years after SBRT, but it then gradually declined over time (Fig. 1C). Among 195 (35.2%) patients who developed recurrence, 28 (18 in KUH, 10 in OCH), 125 (53 in KUH, 72 in OCH), and 42 (31 in KUH, 11 in OCH) patients had LR only, RDR only, and both, respectively. Isolated RDR was the most common recurrence pattern observed as the first progression (133 patients; Fig. 2). Of the 47 patients who initially developed isolated LR, 40.4% (19/47) developed RDR and 36.2% (17/47) died of lung cancer without RDR. The most common transition was from isolated RDR to CSD (84/137 [61.3%]). The rates of transition from isolated LR to CSD and from both LR and RDR to CSD were 12.4% (17/137) and 26.3% (36/137), respectively. Figure 3 shows the number of patients at risk at each landmark point, together with their recurrence status at that time. This time-series recurrence information was used to build the dynamic prediction models for the probability of CSD.

Regarding the salvage treatment for isolated LR (47 patients), 12.8% (6/47) received surgery, 4.3% (2/47) chemoradiotherapy, 6.4% (3/47) cytotoxic chemotherapy, 2.1% (1/47) molecular targeted therapy such as tyrosine kinase inhibitors. The remaining 74.5% (35/47) received best supportive care due to old age or comorbidities.

Dynamic prediction model for cause-specific death

Table 2 shows the regression coefficients and odds ratios (ORs) with 95% confidence intervals (CIs) for the factors included in the landmark model. Among the baseline covariates, older age at SBRT and advanced T stage were significantly associated with increased odds of 3-year dynamic CSD. Meanwhile, sex and histology had no significant effect. Both time-dependent covariates demonstrated strong effects on 3-

year dynamic CSD (LR: OR, 8.5; 95% CI, 6.0–12.0; $P < .001$; RDR: OR, 11.6; 95% CI, 9.1–14.9; $P < .001$). The time elapsed after SBRT (i.e., landmark time) was significantly associated with a decreased risk of subsequent CSD. This is in accordance with Figure 1A, which shows a gradual decrease in the cumulative incidence of CSD over time.

Dynamic probabilities of CSD within 3 years can be predicted according to recurrence status at the time of prediction and baseline characteristics, as shown in Figure 4. For instance, in a 65-year-old male patient with a T1mi–b adenocarcinoma at 2 years after SBRT (Fig. 4A), the probabilities of 3-year dynamic CSD (i.e., CSD between 2 and 5 years after SBRT) were 3.6% if the patient has not developed either RDR or LR at the prediction time, 24.0% if the patient has an isolated LR, 30.2% if the patient has only RDR, and 78.6% if the patient has both LR and RDR. For a male patient with higher baseline risk factors (age 85 years, T2a, and adenocarcinoma, Fig. 4B), the 3-year dynamic CSD probabilities increased to 12.2%, 54.0%, 61.7%, and 93.2%, respectively. For any recurrence status, the 3-year dynamic CSD probabilities decreased with time. For patients with either baseline characteristics, the probability of 3-year dynamic CSD was comparable if they only developed either isolated LR or isolated RDR by the prediction time point; meanwhile, it was markedly higher in patients who developed both LR and RDR.

Discussion

The impact of LR on CSD in patients with ES-NSCLC is still unclear. Our dynamic prediction model clearly shows that LR is a major risk factor for CSD with an OR of 8.5, and the risk is comparable to that of RDR with an OR of 11.6. This finding suggests that

strategies to further improve local control can contribute to better survival in patients with ES-NSCLC.

One of the main advantages of the present study was the estimation of the effect of LR on CSD to properly estimate the causal relationship between LR and death. However, in retrospective studies and meta-analyses, improved local control did not always translate to superior OS (3,6-10). One of the reasons for this inconsistency may be the high incidence of comorbidities in the SBRT population (9). In addition, even in clinical trials, the patients were aged an average of > 70 years, and less than 50% of all deaths were due to lung cancer (4,20). As the safety and efficacy of SBRT have been recognized, an increasing number of patients at high risk of NSD have become eligible for SBRT. Hence, given our results showing the clear impact of LR on CSD, it would be helpful to use data from randomized studies or data that are sufficiently adjusted for the risk of NSD when examining the effects of different SBRT doses on OS. In a propensity score-matched cohort study by Tateishi et al., a higher BED improved not only local control, but also CSD and OS without increased toxicity in ES-NSCLC (21). Although there are no randomized studies available, the ongoing Japan Clinical Oncology Group Study protocol 1408, a prospective randomized phase III study comparing between 55 Gy in four fractions and 42 Gy in four fractions, is expected to clarify the safety and efficacy of increasing SBRT doses above a BED of 100 Gy (22).

Another advantage of this prediction model is that it incorporates the respective timing of LR and RDR, allowing us to estimate the relative impact of both events on the CSD. Meanwhile, the standard “static” model has difficulty incorporating multiple intermediate events. Therefore, only the first recurrence is usually evaluated for its correlation with mortality (23). As in previous reports (18,24,25), RDR was the

predominant pattern of the first failure (Fig. 2), suggesting that isolated RDR included occult metastases that were present at the time of diagnosis or metastases that grew before LR became apparent. Even if the metastatic site is the main site of the first recurrence, dynamic prediction helps us to evaluate the significance of LR.

In many cancer types, a shorter interval to recurrence has been reported to be associated with resistance to treatment and a shorter prognosis (26,27). For example, Viani et al. found that a shorter interval time between the first radiotherapy and re-SBRT was associated with inferior survival in lung cancer patients (28). In our study, the dynamic probability of CSD gradually decreased with time, indicating that the period of time a patient has already survived may influence the patient's subsequent prognosis (Fig. 4). Although we did not evaluate the role of salvage treatment, our findings have the same implications as those of Viani et al. and support that dynamic prediction allows making specific inferences about the effect of the elapsed time.

To the best of our knowledge, our study is the first to use dynamic prediction to challenge clinical questions in the field of radiation oncology. Similar models have been used for the dynamic prediction of survival, for example, in patients with breast cancer (29) and leukemia (30). Dynamic prediction has been used to determine the individual benefit of continued hormone therapy (29) and discontinued immune suppression (30). Dynamic prediction refers to how prognosis changes over time, considering information on clinical events and/or biomarkers available during follow-up. This personalized prediction using existing data would provide valuable information in daily clinical practice, for example, when we are considering treatments for recurrence.

However, we also acknowledge that there are some limitations and inherent biases arising from this retrospective study. First, our dynamic prediction model relies on the

frequency and timing of relapse events. We recorded the second and subsequent recurrences. However, if a patient has life-threatening metastases and/or is receiving palliative care, frequent imaging studies to detect LR are not always performed; thus, the incidence of LR might be underestimated and consequently affect the model. Second, although the number of cases in this study was not small for an observational study of SBRT for ES-NSCLC, there were some limitations in the analysis because of the limited data. We chose 4 years after SBRT as our last prediction time point, delayed recurrences have been reported even after 4 years of SBRT (24,25), and the effect of such late recurrence on CSD is unknown. Furthermore, our model did not include factors that affect survival, such as the smoking status or pulmonary function. In addition, salvage treatment could not be included in the model, because it is a dynamic variable whose value changes like those of LR and RDR, and also, the recurrence status changes from "yes" to "no", which could complicate the model. Third, we could not completely rule out the direct effect of BED on CSD in this study framework. We chose LR status instead of BED for our model in order to focus our evaluation on the association between LR and CSD, which is an unanswered clinical question in SBRT for ES-NSCLC. In our cohort, higher BED may have indirectly contributed to the reduction of CSD via the local control, considering the strong correlation between BED and LR rates, which has been demonstrated in several reports (3,6-10). Therefore, if BED had a direct effect on CSD, we believe the effect would have been small. Due to the above-listed limitations of the study, patients' survival may vary depending on the treatment era, treatment strategies, and patient background, at each institution. To address these limitations of our model, future research is required to test the framework and improve the generalizability of our model, including external validation, to examine the predictive performance of the dynamic prediction models for competing risks.

Conclusion

The dynamic prediction model showed that LR is a major risk factor for CSD in patients with ES-NSCLC treated with SBRT, and the risk is comparable to that from RDR. This suggests that further improved local control is desired, for example, by dose escalation or modification of the dose distribution in the PTV, in these patients.

Table 1. Baseline characteristics of patients

Characteristic	Overall (n=535)	KUH (n=205)	OCH (n=330)	p-Value [†]
Follow-up time, median (IQR), y	4.1 (2.3, 6.2)	3.9 (2.0, 6.8)	4.2 (2.4, 6.0)	0.794
Age, median (IQR), y	78 (74, 83)	78 (73, 83)	78 (74, 83)	0.997
Sex (%)				0.237
M	385 (72.0)	154 (75.1)	231 (70.0)	
F	150 (28.0)	51 (24.9)	99 (30.0)	
PS (%)				0.725
0–1	493 (92.1)	189 (92.2)	304 (92.1)	
2	42 (7.9)	16 (7.8)	26 (7.9)	
T stage (%)				0.158
T1mi	2 (0.4)	0 (0)	2 (0.6)	
T1a	21 (3.9)	5 (2.4)	16 (4.8)	
T1b	193 (36.1)	79 (38.5)	114 (34.5)	
T1c	165 (30.8)	70 (34.1)	95 (28.8)	
T2a	154 (28.8)	51 (24.9)	103 (31.2)	
Histology (%)				<0.001
Adenocarcinoma	180 (33.6)	80 (39.0)	100 (30.3)	
SCC	107 (20.0)	62 (30.2)	45 (13.6)	
Other	48 (9.0)	23 (11.2)	25 (7.6)	
Unproven	200 (37.4)	40 (19.5)	160 (48.5)	
CCI (%)				0.484
0–1	357 (66.7)	141 (68.8)	216 (65.5)	
≥2	178 (33.3)	64 (31.2)	114 (34.5)	
BED*, Gy (%)				<0.001
100–135	229 (42.8)	205 (100.0)	24 (7.3)	
140–175	180 (33.6)	0 (0)	180 (54.5)	
220–300	126 (23.6)	0 (0)	126 (38.2)	

Abbreviations: KUH, Kyoto University Hospital; OCH, Ofuna Chuo Hospital; IQR, interquartile range; PS, Performance Status; SCC, Squamous cell carcinoma; CCI, Charlson comorbidity index; BED, biologically effective dose

* Dose at the maximum or the isocenter

† Chi-squared test or Fisher exact test for proportions and Mann–Whitney U test for medians

Table 2. Landmark model for cause-specific death

Covariate	Coefficient	OR [†]	95% CI	<i>p</i> -Value
Age at SBRT (ref: 75 years)				
per 10 years	0.43	1.53	1.30–1.81	<0.001
Sex (ref: F)				
M	-0.19	0.83	0.66–1.03	0.092
T stage (ref: T1mi–T1b)				
T1c	0.41	1.50	1.18–1.93	0.001
T2a	0.46	1.59	1.23–2.03	<0.001
Histology (ref: Adenocarcinoma)				
Non-adenocarcinoma	0.094	1.10	0.84–1.44	0.493
Unproven	-0.17	0.84	0.66–1.07	0.166
LR (ref: No recurrence)				
Yes	2.13	8.45	5.98–11.96	<0.001
RDR (ref: No recurrence)				
Yes	2.45	11.61	9.07–14.85	<0.001
Landmark time*				
per 1 year	-0.26	0.77	0.68–0.87	<0.001

* Time elapsed since 1year after SBRT

† The exponential of each regression coefficient

Abbreviations: OR; odds ratio; CI, confidence interval, SBRT, stereotactic body radiotherapy; LR, local recurrence; RDR, regional/distant recurrence

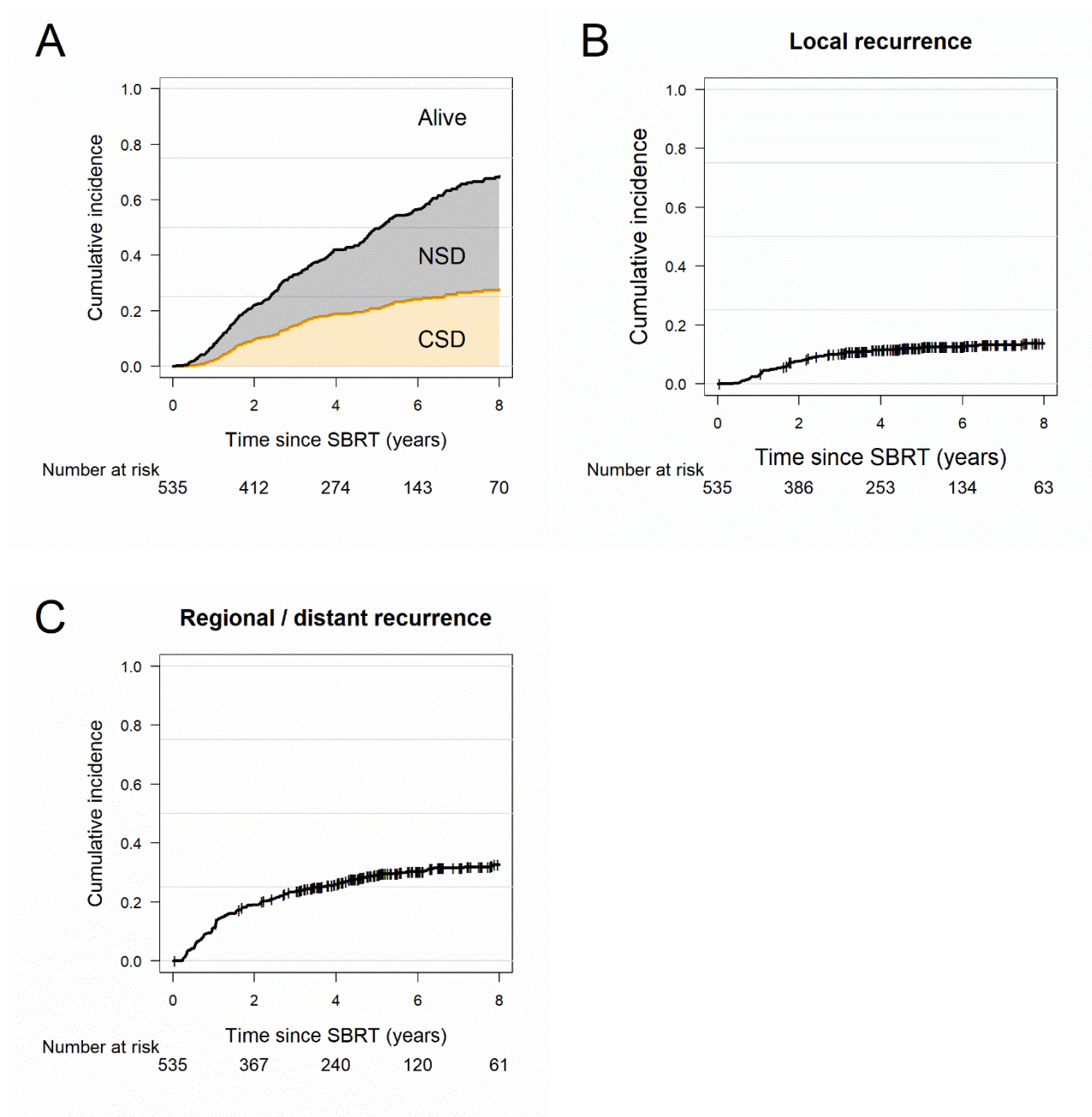


Fig. 1.

Cumulative incidences of study outcomes. Cause-specific death (CSD) and non-specific death (NSD) (A). Local recurrence (B). Regional/distant recurrence (C).

Abbreviation: SBRT, stereotactic body radiotherapy

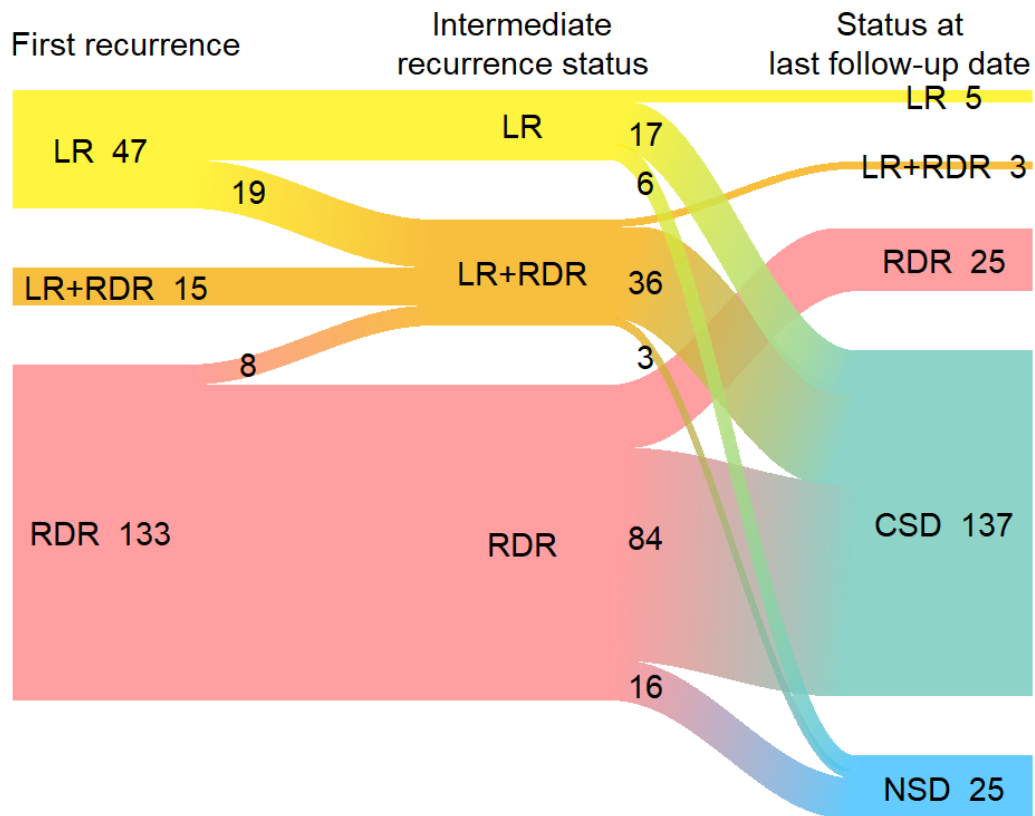


Fig. 2.

Sankey diagram showing the transition of events in patients who developed recurrence (n = 195). The left, middle, and right indicate the site of first recurrence, the intermediate status of recurrence, and the status at the last follow-up date, respectively.

Abbreviation: LR, local recurrence; RDR, regional and/or distant recurrence (RDR); CSD, cause-specific death; NSD, non-specific death

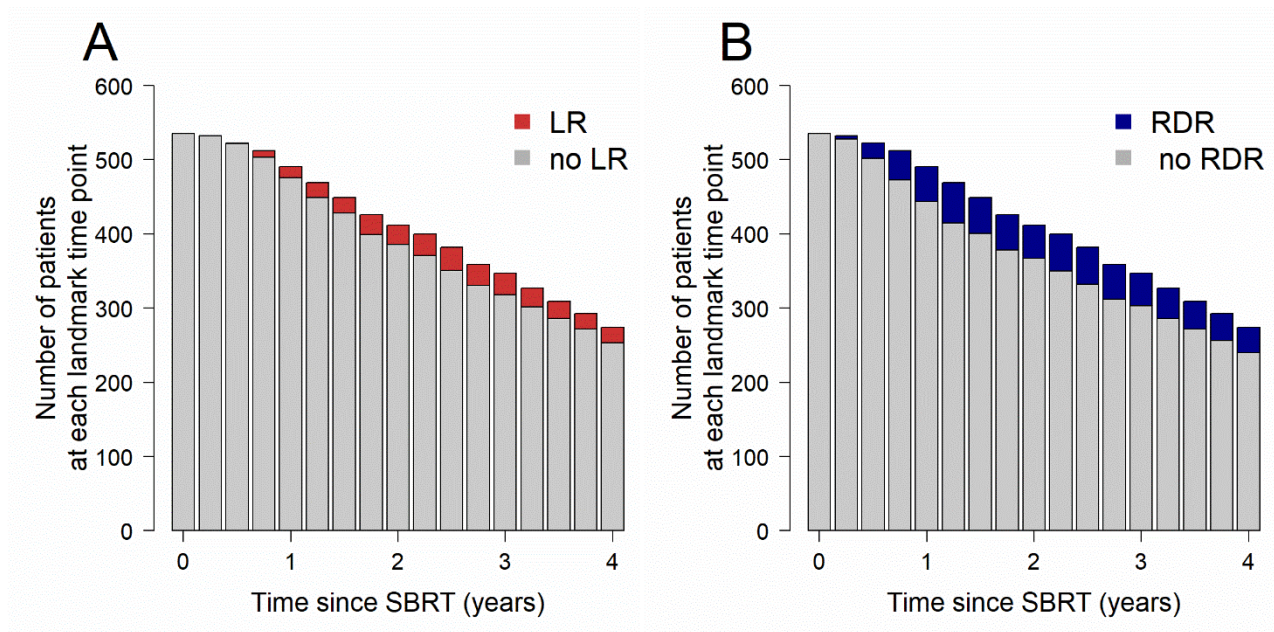


Fig. 3.

Number of patients at risk at each landmark time point together with information about their recurrence status at that time. (A) Red, patients with local recurrence (LR); gray patients without LR. (B) Blue, patients with regional and/or distant recurrence (RDR); gray, patients without RDR.

Abbreviation: SBRT, stereotactic body radiotherapy

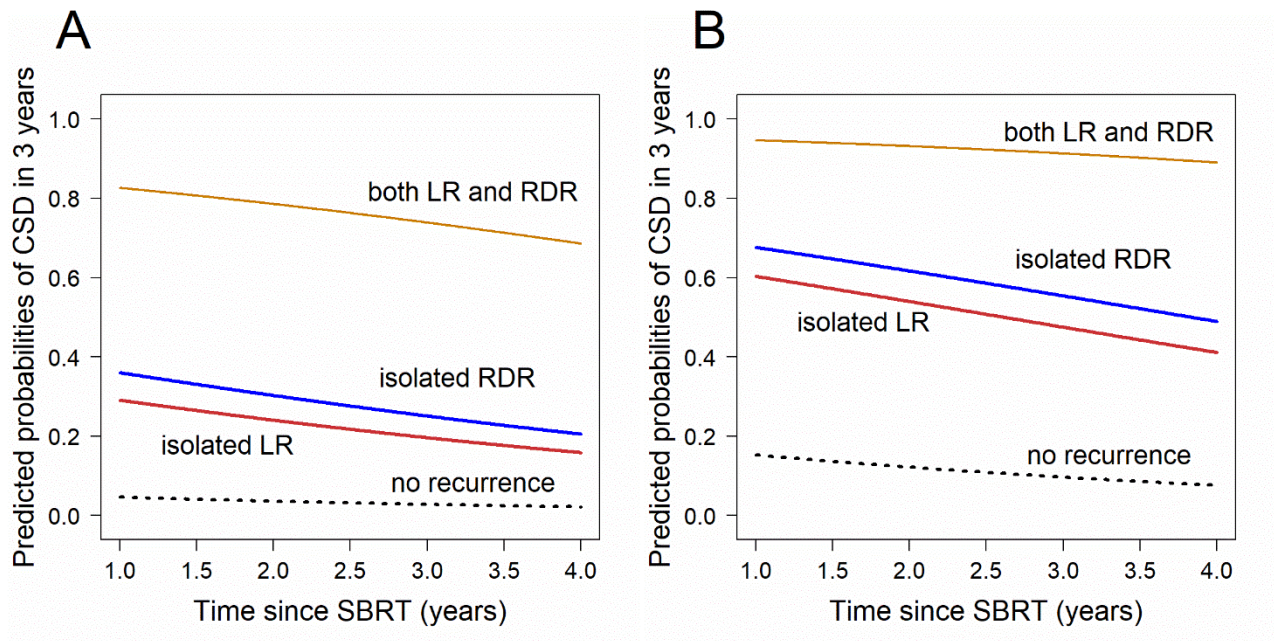


Fig. 4.

Dynamic probabilities of cause-specific death (CSD) within 3 years of the prediction time points for patients with different characteristics and at different recurrence status. A 65-year-old male with stage T1mi-b adenocarcinoma at the time of stereotactic body radiotherapy (SBRT) (A). An 85-year-old male patient with stage T2a adenocarcinoma at the time of SBRT (B). The four colored lines represent the following recurrence status that the patient developed by the time of prediction: black, no recurrence; red, isolated local recurrence (LR); blue, isolated regional and/or distant recurrence (RDR); and yellow, both LR and RDR. The range on the horizontal axis corresponds to that of the landmark points.

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