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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Mortality after radiotherapy or surgery in the treatment of early stage non-small-cell lung cancer: a population-based study on recent developments

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Abstract

Background Stereotactic body radiotherapy (SBRT) can achieve high tumour control with limited toxicity for inoperable early stage non-small-cell lung cancer (NSCLC) patients.

Patients and methods The German Epidemiologic Cancer Registries from the Robert-Koch Institute were assessed. Periods according to the availability of SBRT were: (1) 2000–2003 (pre-SBRT); (2) 2004–2007 (interim); and (3) 2007–2014 (broad availability of SBRT). To assess the association of cancer-related parameters with mortality, hazard ratios (HR) from Cox proportional hazards models were computed. To evaluate the change of treatment-related mortality, we performed interaction analyses and the relative excess risk due to interaction (RERI, additive scale) was computed.

Results A total of 16,292 patients with UICC stage I NSCLC diagnosed between 2000 and 2014 were analysed. Radiotherapy utilization increased from 5% in pre-SBRT era to 8.8% after 2007. In univariate analyses, survival in the whole cohort improved only marginally when 2000–2003 is compared to 2004–2007 (HR 0.92, 95% CI 0.85–1.01) or 2008–2014 (HR 0.93, 95% CI 0.86–1.01). Comparing surgery/radiotherapy, mortality in the radiotherapy group started from a 3.5-fold risk in 2000–2003 to 2.6 after 2007. The interaction analysis revealed a stronger improvement for radiotherapy (multiplicative scale for 2000–2003 vs. > 2007: 0.74, 95% CI 0.58–0.94). On an additive scale, treatment × period interaction revealed an RERI for 2000–2003 vs. > 2007 of − 1.18 (95% CI − 1.8, − 0.55).

Conclusions Using population-based data, we observed a survival improvement in stage I lung cancer over time. With an increasing utilization of radiotherapy, a stronger improvement occurred in patients treated with radiotherapy when compared to surgery.

Keywords Stereotactic body radiotherapy · Lung cancer · Stage I · Non-small-cell lung cancer · Radiotherapy · Patterns of care · Population-based analysis

Abbreviations

UICC	Unité international contre le cancer
NSCLC	Non-small-cell lung cancer
VATS	Video-assisted thoracoscopic surgery
SBRT	Stereotactic body radiotherapy
OS	Overall survival
RT	Radiotherapy
RKI	Robert-Koch Institute
HR	Hazard ratio
Ci	Confidence interval
SCLC	Small-cell lung cancer
ECOG	Eastern Co-operative Oncology Group

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Introduction

Lung cancer accounts for a high proportion of worldwide cancer mortality (Goldstraw et al. 2007; Siegel et al. 2016). Over the last decades, however, improvements in overall survival

remained rather small (Rami-Porta et al. 2009) with highly varying treatment patterns across different countries.

For early stage (UICC I) non-small-cell lung cancer (NSCLC), surgery is the standard of care with video-assisted thoracoscopic (VATS) lobectomy as the therapeutic approach of choice. However, a significant part of stage I NSCLC is either surgically or medically inoperable due to tumour location, operative risk, age, frailty, or comorbidities (Cykert et al. 2010; Wisnivesky et al. 2005; Vest et al. 2013). In the past, conventional radiotherapy was the only treatment option for the latter patients, providing a slightly improved survival compared to the group that received neither radiotherapy nor surgery (Wisnivesky et al. 2005; Vest et al. 2013).

With the introduction of stereotactic body radiotherapy (SBRT), which is a high precision image-guided form of radiotherapy (RT) characterized by the application of few fractions of high biologic effective doses to small tumour volumes (Guckenberger et al. 2014), tumour control and outcome could be significantly improved (Guckenberger et al. 2013). Local control rates after SBRT are reported > 90% with limited toxicity (Guckenberger et al. 2013) which makes this treatment a well suitable and tolerable option for elderly patients and those with clinically relevant comorbidities (Shirvani et al. 2013; Palma et al. 2010).

To analyse and assess the impact of the introduction of new treatments, population-based studies are a valuable tool (Palma et al. 2010). In The Netherlands, Haasbeek et al. (2012) showed a population-based increase in survival of elderly early stage NSCLC patients receiving SBRT. Similarly, Palma et al. (2010) reported a 16% absolute increase in RT use, an improved overall survival (OS), and a decline in the number of untreated patients after the introduction of SABR for 75+-year-old NSCLC stage I patients in The Netherlands.

Despite the fact that after the year 2000, German radiation oncology centres rapidly adopted SBRT as an alternative treatment for stage I NSCLC patients (Guckenberger et al. 2013), there are no population-based data on the impact of the introduction of SBRT in Germany available so far. The aim of this study is to evaluate the treatment utilization and the temporal change in OS associated with radiotherapy when compared to surgery on an aggregated level for stage I NSCLC in the German population. SBRT among other medical improvements might have primarily triggered such survival effects.

Methods

Data and material

We used data from the German Epidemiological Cancer Registries provided by the Robert-Koch Institute (RKI) for public use. This population-based registry incorporates federal data that are transferred to the RKI.

The data set contains, amongst other information, data on grading and histology, TNM stage, cause and date of death, date of birth, and date of diagnosis (month as the smallest temporal unit in each date variable) and treatment. However, information on performance status, comorbidities, or further details on treatment procedures such as the administered radiation dose or fractionation are not included. In addition, the TNM stage in this data set refers to the clinical or pathological stage (if an operation was performed), while there is no information on the clinical stage in cases, where a p-stage is available (Hager et al. 2015).

We considered cases of lung cancer for further analyses if they had a TNM stage (clinical or pathological) of T1/2a and N0/*x* and M0/*x* corresponding to an UICC I. Subsequently, we excluded cases with a small cell histology, that is, a morphologic code of the ICD-O of 8021, 8020, 8041, 8042, 8043, 8044, or 8045. Likewise, patients were excluded if both, surgery and radiotherapy, were recorded as a treatment, cases were diagnosed by means of an autopsy or the diagnosis was merely based on a death certificate. Finally, 16,292 cases were considered for multivariate analyses (Figure S1).

Definition of periods

According to a survey considering nearly all radiotherapy institutions in Germany (Guckenberger et al. 2013), the application of SBRT increased continuously between 1998 and 2011, while more than 100 cases were treated for the first time in Germany in 2004 and more than 300 in 2008 (cumulative numbers). In our analyses, cases diagnosed between 2000 and 2014 (most recent data with sufficient quality) were included. Thus, we defined the time between 2000 and 2003 as a low availability—era, 2004–2007 as a transition period and the time after 2007 as the time when SBRT was widely available. Cases were censored at January of 2015 (latest complete recording of death) or after 84 months to avoid a bias due to cases that died in more recent years, but whose changed survival status had not yet been considered in the data, which would lead to a biased, more favourable survival situation in the period after 2007.

Grade definition

Grade categories were defined as low grade [grade 1, 2 and low/medium grade (definition according to the 'Arbeitsgemeinschaft Deutscher Tumorzentren, ADT)]; high grade [grade 3,4 and high grade (ADT definition (Stegmaier et al. 2018))], and unknown.

Statistical analyses

We used proportional hazard Cox-regression models to assess the association of cancer-related parameters with mortality and computed hazard ratios (HR) with 95% confidence intervals (CI).

To compare the change of treatment-related mortality (surgery and radiotherapy) with time, we performed an interaction analyses, both on the multiplicative and additive scale (Knol et al. 2011; Vittinghoff and McCulloch 2007). Here, we included all patients of all periods in one Cox-regression model adding a period × treatment interaction term in addition to the main effect of period, treatment, and covariates (see below). This term estimates possible differences in hazards related to treatment between periods statistically. Thus, based on the assumption of proportional hazards, as it is required by Cox-regression models, treatment differences between periods can be compared directly in one model.

In more detail, interaction refers to the situation when the effect size of one factor is dependent on the presence of another or is modified by it. In our study, this can be translated to the situation when the treatment effect (radiotherapy vs. surgery) is dependent on the period when the patient was diagnosed with lung cancer. Now, if the combined risk excess of treatment and period (interaction) is larger the sum of the individual effects of treatment and period (main effects), we observe interaction on an additive scale. In contrast, when the combined effect is larger than the product of the main effect, interaction on a multiplicative scale is present. The basic concept of additive interaction is illustrated in the following example: Suppose that there is a risk factor A with a relative risk for death of 1.6 (risk excess = 0.6) when present and a second factor B with a relative risk of 1.4 (risk excess = 0.4). On an additive scale, when both risk factors are present, we would compute a combined risk excess of 1.0. However, if the absolute risk is even larger, say a relative risk of 2.4 (risk excess = 1.4), this additional risk can be attributed to the interaction of both factors. From a public heath perspective, this scale seems more appropriate as risk factors with large relative risk might easily confound an apparent interaction due to their exponential increase when they are multiplied. In the interaction analyses, we only included subjects who underwent surgery or radiotherapy. We computed the 'Relative Excess Risk Due to Interaction' (RERI, an RERI < 0 indicates a risk reduction, see the appendix for a description), which quantifies interaction on an additive scale, according to Knol et al. (2011).

Finally, all models were adjusted for histologic grade (as defined above), age (polynomials of age squared and square root of age were test by means of a log-ratio test, but the model was not improved significantly when they were considered), histologic confirmation, T-stage (T1 vs. T2a), and patient sex. We also considered interactions of these variables with periods, but found no significant model improvement when a log-ratio test was performed.

During the studied period (2000–2014), the TNM version change from 5 to 6 (since 2002) did not result in an alteration of the TNM stage for considered patients (only T1 included). TNM version 7 (since 2009) introduced the new levels of T1a and T1b and additionally T2a, while patients with the latter stage might also be candidates for SBRT. To ensure comparability of the patients between periods, we adjusted for T2a stage as a separate category in the statistical analyses.

Bias and sensitivity analyses

As some German registries only started to record incident cases after 2007, the sample size is markedly higher in the most recent period when compared to the previous ones. This might result in a bias of the period-related treatment effect if, e.g., cases are younger or healthier between periods and treatments. Finally, this can be assessed statistically by, e.g., considering a period × age interaction in multinominal logistic regression models with period as the outcome. Here, as the clinical performance status (according to Eastern Cooperative Oncology Group, ECOG) was not available, the most valuable parameter is age, which we used as a surrogate parameter to access the period-related bias in the model (models included age, sex, treatment as main effects, and age × treatment, sex × treatment interaction terms).

Furthermore, as a sensitivity analysis, we included only registers from federal states with a continuous registration activity during the study period (2000–2014) distinguishing themselves from other registries by a higher data quality and longer recording time (East Germany including Berlin, Bavaria, Schleswig-Holstein, and Rhineland-Palatinate). Another sensitivity analysis assessing the treatment and period effect on overall survival was performed in the age group of 75 years or older.

A significance level of 5% was used. All statistical analyses were performed using SAS, version 9.4.

Results

Databank search and case selection

The databank search yielded a total of 28.089 UICC I stage lung cancer cases (cases were reported in accordance with international guidelines, see http://www.iacr.com.fr/) diagnosed between 2000 and 2014 from which the SCLC cases were excluded (Figure S1 of the supplement). In the next step, cases with both RT and surgery as the treatment or with missing treatment variables were removed, yielding a total of 16,475 cases. Finally, we excluded cases with

diagnosis from autopsy/death certificate which resulted in a final number of 16,292 cases that we used for multivariate analyses (16,467 cases for crude analyses). Median survival times in the group with neither treatment were 25 months (95% CI 18–33 months) between 2000 and 2003, 30 months (95% CI 20–39 months) between 2004 and 2007 and 29 months (95% CI 25–33 months) after 2007. For the radiotherapy group, the median survival was 25 months (95% CI 21–29 months) between 2000 and 2003, 31 months (95% CI 24–36 months) between 2004 and 2007, and 30 months (95% CI 28–34 months) after 2007. Finally, for patients treated with surgery, the median survival was not reached in either period (see Table S1 for further survival statistics).

Patient characteristics

Regarding the distribution of considered treatments, we found a higher proportion of cases treated with radiotherapy after 2007 of 8.8% (95% CI 8.3–9.3%) when compared to earlier times, where the proportion was only around 5% (period 1: 5.9%, 95% CI 4.8–7.0%; period 2: 5.0%, 95% CI 4.1–5.8%; Fig. 1). In relative terms, patients treated with radiotherapy or who received neither treatment were markedly older and more likely to be men when compared to proportions in the surgery group (Table 1). For all treatment groups, pathologic confirmation was obtained in the majority of cases with the rate of available histologic confirmation of diagnosis being highest in those treated by surgery. The number of cases who received either radiotherapy or neither surgery nor radiotherapy in clinical stage T1 or T2a was lower than the proportion who received surgery. Considering all lung cancer stages, the proportion of UICC I cases did not decrease over time (Table 1). In addition, we observed an improved survival across periods when all lung cancer cases are considered (Table 1).

Survival analyses

Table S1 of the supplement shows descriptive mortality data of the considered cohort. Most remarkably was an increase of the 4-year survival rate in the group with radiotherapy for the years after 2007 up to 40.0% when compared to the years between 2000 and 2003 (27.6% for 2004–2007).

In univariate survival models, when the period between 2000 and 2003 was compared to the latest period of 2008 to 2014, we found an improved survival in patients who underwent radiotherapy (HR of period effect: 0.76, 95 CI 0.62–0.97; Fig. 2), while the null effect value was included in the confidence interval for cases with neither treatment nor surgery. Effect estimates changed only slightly when we adjusted for the treatment effect.

In the association of treatment with mortality, we found that the cases of the surgery group had the lowest mortality risk compared to the two remaining groups (Fig. 3, e.g., HR 2.7 after covariate adjustment for the comparison of radiotherapy and surgery) ranging around a hazard ratio of three. Independently from period and considered covariates, we computed the mortality risk of the radiotherapy group to be 2.56-fold (95% CI 2.3–2.85) the risk of the surgery group at the most recent period.

Coming to multivariate analyses, a cancer diagnosis after 2007 was associated with a lower mortality risk in all cases irrespective of the treatment received when compared to a diagnosis in or before 2007 (HR 0.83 95% CI 0.75–0.91, Table 2).

In stratified analyses, patients in the radiotherapy group experienced a strong improvement (HR 0.7, 95% CI 0.55–0.88, Table S2).

In the interaction analysis (comparing radiotherapy and surgery in terms of a change in survival across periods), we observed a stronger improvement in overall survival after 2007 when compared to the years of 2000 to 2003 in the radiotherapy group (Table 2) than in cases with surgery or neither treatment for all cases irrespective of

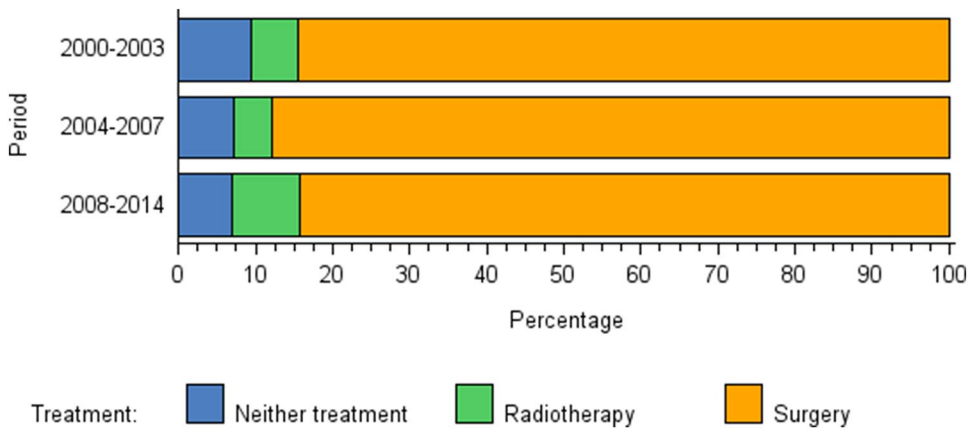

Fig. 1 Proportion of administered treatments in relation to period of diagnosis

Table 1 Patient characteristics in the study cohort in relation to year of diagnosis and treatment

	2000–2003			2004–2007			2008–2014		
	n (percentage)			*n* (percentage)			*n* (percentage)		
	Neither treatment	Radiotherapy	Surgery	Neither treatment	Radiotherapy	Surgery	Neither treatment	Radiotherapy	Surgery
Age	69.9 (68.4–71.3)	68.9 (67.4–70.5)	64 (63.5–64.5)	69.8 (68.5–71.1)	71.5 (70.1–73)	65.9 (65.5–66.3)	72.5 (71.9–73.2)	72.7 (72.2–73.2)	66.9 (66.7–67.1)
Age quantiles: 10%/25%/50%/70%/90%	57/65/70/77/81	59/64/69/74/78	51/59/65/71/75	57/64/70/77/82	61/66/73/77/82	53/61/67/73/77	59/67/74/79/84	60/67/74/79/83	54/61/68/74/78
Survival status[a]									
Alive	38 (22.1)	8 (7.5)	883 (57.7)	51 (27.7)	13 (10.4)	1314 (58.6)	424 (50.8)	596 (57)	8022 (79.8)
Dead	134 (77.9)	99 (92.5)	647 (42.3)	133 (72.3)	112 (89.6)	929 (41.4)	410 (49.2)	450 (43)	2029 (20.2)
Sex									
Male	123 (71.5)	85 (79.4)	1057 (69.1)	121 (65.8)	97 (77.6)	1493 (66.6)	581 (69.7)	763 (72.9)	6292 (62.6)
Female	49 (28.5)	22 (20.6)	473 (30.9)	63 (34.2)	28 (22.4)	750 (33.4)	253 (30.3)	283 (27.1)	3759 (37.4)
T-stage									
T1	171 (99.4)	107 (100)	1528 (99.9)	181 (98.4)	125 (100)	2233 (99.6)	562 (67.4)	685 (65.5)	7094 (70.6)
T2a	1 (0.6)	0 (0)	2 (0.1)	3 (1.6)	0 (0)	10 (0.4)	272 (32.6)	361 (34.5)	2957 (29.4)
Pathologic confirmation									
Yes	152 (88.4)	104 (97.2)	1524 (99.6)	158 (85.9)	118 (94.4)	2234 (99.6)	694 (83.2)	904 (86.4)	10,005 (99.5)
No	20 (11.6)	3 (2.8)	6 (0.4)	26 (14.1)	7 (5.6)	9 (0.4)	140 (16.8)	142 (13.6)	46 (0.5)
Grade									
Low	49 (28.5)	35 (32.7)	794 (51.9)	59 (32.1)	38 (30.4)	1257 (56)	260 (31.2)	323 (30.9)	5655 (56.3)
High	31 (18)	21 (19.6)	352 (23)	38 (20.7)	24 (19.2)	624 (27.8)	201 (24.1)	226 (21.6)	3317 (33)
Unknown	92 (53.5)	51 (47.7)	384 (25.1)	87 (47.3)	63 (50.4)	362 (16.1)	373 (44.7)	497 (47.5)	1079 (10.7)
Median survival	25 (18–33)	25 (21–29)	Not reached	30 (20–39)	31 (24–36)	Not reached	29 (25–33)	30 (28–34)	Not reached
Proportion of UICC I	2623/16,938 (15.5)			3742/23,746 (15.8)			13,926/64,947 (21.4)		
Median survival (all cases of lung cancer)[b]	22 (22–23)			25 (25–26)			32 (32–33)		

For age, the median and the 25% and 75% quantile (in brackets) are provided. For further categorical variables, the percentages are provided in brackets. *P* values were derived from Chi-square test

[a]Percentage of patients alive from all cases are given in brackets for the respective period and treatment group (e.g., in period 2000–2003 and neither radiotherapy/surgery this is 38/(134 + 38) = 22.1%)

[b]Months (95% confidence interval) in the entire cohort

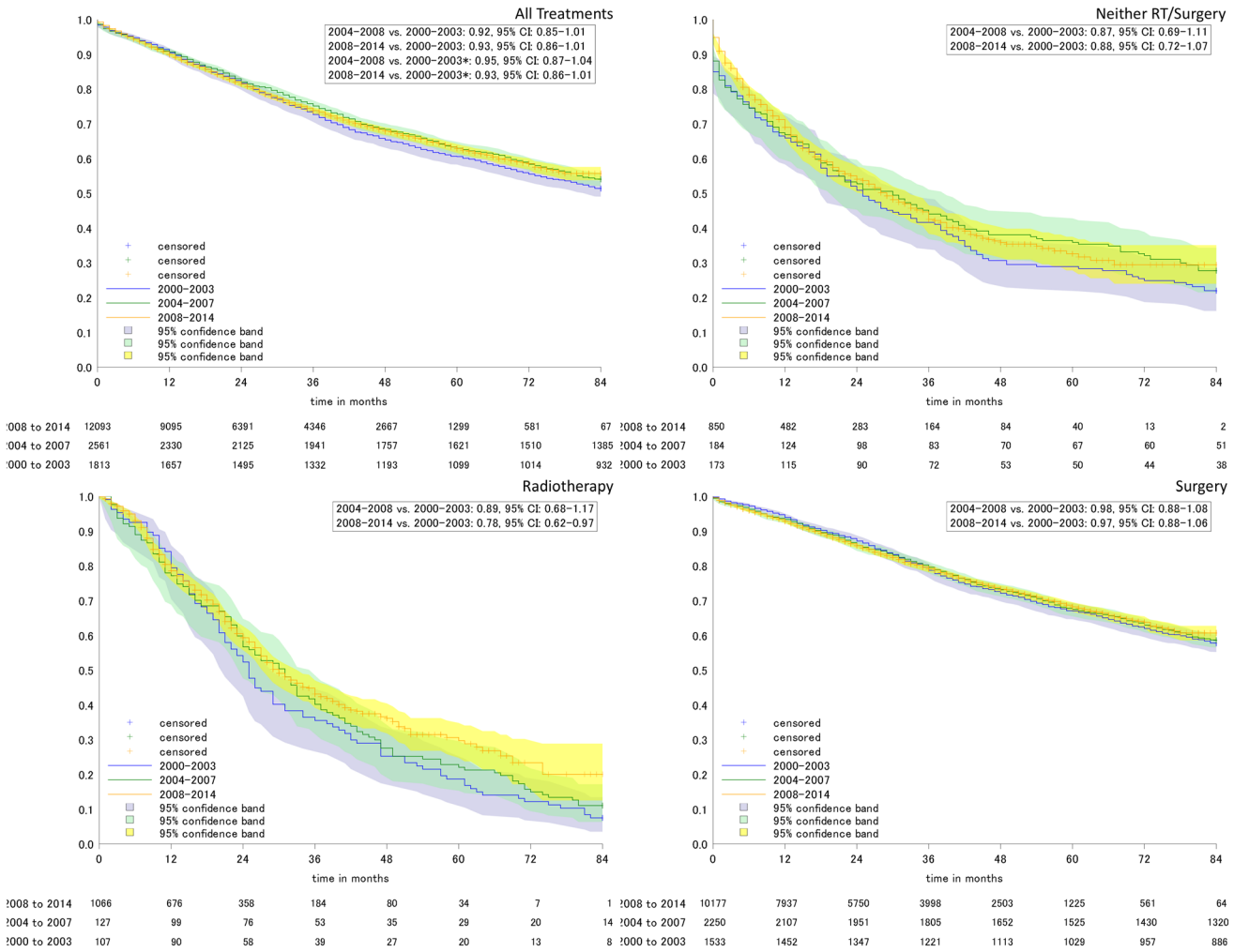

Fig. 2 Kaplan–Meier curve and survival analyses from Cox-regression models of overall survival in relation to period and treatment (univariate analyses)

sex. Here, we found a significant change in the treatment effect (radiotherapy vs. surgery) on both the multiplicative (HR for interaction: 0.74, 95% CI 0.58–0.94, risks are added, Table 2) and the additive scale (RERI − 1.18, 95% CI − 1.80 to − 0.55, risks are multiplied). In contrast, there was no change in the estimates of neither treatment compared to surgery across considered periods (Table 2). In sex-specific analyses, we found an improved survival across periods in men and women. However, effect estimates of interaction analyses were close the null effect value and confidence intervals wider in women when compared to men (men: 0.7, 95% CI 0.54–0.91, women: 0.9, 95% CI 0.53–1.53).

Bias and sensitivity analyses

Using a logistic regression model with the period as the outcome variable including an age- and sex × treatment interaction, we found that both the age- and sex × treatment interactions were not significantly related to any of the considered periods (response variable in the logistic regression model).

When the registries with a higher data quality were considered (Table S3), we found similar estimates as in the analysis of the whole cohort. Most importantly, there remained strong evidence for a treatment × period interaction on an additive scale (RERI for period 2000–2003 vs. > 2007: − 1.2, 95% CI − 1.86, − 0.54). On a multiplicative scale the HR of the treatment × period effect for period 1 vs. 3 (0.77, 95% CI 0.6–0.98) remained virtually unaltered when compared to the complete data set, while confidence intervals were wider.

In patients aged 75 years or older, we found a lower risk of death in the period after 2007 when compared to the time between 2000 and 2003 (HR 0.76, 95% CI 0.62–0.94), which was not the case for the years between 2004 and 2007 (HR 0.82, 95% CI 0.66–1.03, see Table S4 in the supplement).

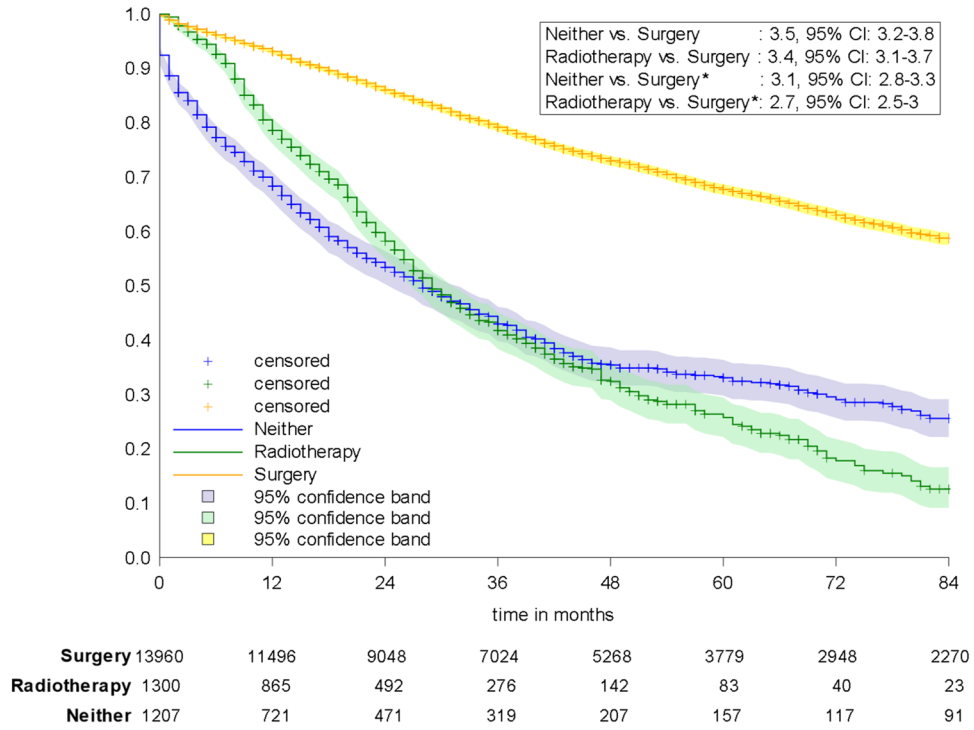

Fig. 3 Kaplan-Meier curves and survival analyses from Cox-regression models in relation to treatment (outcome: overall survival)

This effect differed not between radiotherapy and surgery or surgery and neither treatment.

Discussion

In our study, the proportion of cases treated with radiotherapy increased between considered periods. Survival of the whole cohort of stage I lung cancer patients improved only slightly between periods.

When compared to surgery, survival improvement was stronger in cases treated with radiotherapy on both, the additive and multiplicative scale, in men. The additive scale might have an especially profound impact in public health when questions of resource allocation are concerned. Focussing on the risk assessment from a patient perspective, the multiplicative scale might be of equal importance. There are situations when there is an interaction on a multiplicative scale, but not on an additive scale and vice versa. This emphasizes the need to compute both scales, which were both significant in our study. However, the main effect comparisons between both treatments remain challenging. As the interaction estimates provide the numerical modification of the radiotherapy vs. surgery effect by period after adjusting for the mentioned confounders estimates might change after the inclusion of further parameters related to the choice of treatment and outcome such as the performance status or comorbidities. The explanation of sex difference might follow the same line. A worse survival prospect and health status in men compared to women might make them the main beneficiaries of emerging technologies targeted at patients unfit for surgery or conventional radiotherapy. A risk of death in women half the size of the risk in men underlines this reasoning. Furthermore, fewer female cases and recorded events in women make it difficult to detect survival differences statistically. The lower mortality of women found in our study stands in line with the general population-based survival rates of German lung cancer patients, where male patients have a significantly inferior survival compared to female patients (Eberle et al. 2015).

The surgery group showed the lowest mortality risk across considered treatments, which might, however, be biased, as this group is highly selective in terms of a better performance status and fewer comorbidities. Such a disadvantageous survival prospect might become especially apparent in times when stereotactic radiotherapy is widely available, as they provide a fast non-invasive treatment option for patients in a poor health condition. This would eventually lead to an underestimation of the period effect in the patient cohort treated by means of radiotherapy.

Population-based survival data of German lung cancer patients show a clear dependence on stage, where UICC stage Ia patients have a 5-year survival rate of 64.9/73.9% (male/female) and stage Ib patients of 53.1/64.2% (male/female) (Eberle et al. 2015).

In our data set, survival improved for cases that were treated with either surgery or radiotherapy in the period when SBRT was available compared to the period of

Table 2 Multivariate Interaction analyses comparing surgery and radiotherapy in terms of overall mortality

Main effects	Both sexes		Men		Women	
	HR (95% CI)	*p* value				
Ref: G1/2						
G3/4	1.33 (1.25–1.42)	< 0.0001	1.23 (1.15–1.33)	< 0.0001	1.78 (1.55–2.03)	< 0.0001
Grade unknown	1 (0.92–1.08)	0.9872	0.99 (0.9–1.09)	0.8426	1.04 (0.89–1.22)	0.6216
Ref: T1						
T2a	1.13 (1.04–1.22)	0.0026	1.1 (1–1.2)	0.039	1.22 (1.04–1.44)	0.0163
Ref: male						
Female	0.58 (0.55–0.62)	< 0.0001	1		1	
Ref: histo+						
No hist	0.97 (0.82–1.15)	0.7312	0.9 (0.73–1.09)	0.2725	1.24 (0.89–1.73)	0.2098
Ref. surgery						
Neither treatment	2.88 (2.39–3.48)	< 0.0001	3.05 (2.46–3.78)	< 0.0001	2.32 (1.57–3.44)	< 0.0001
Radiotherapy	3.47 (2.8–4.29)	< 0.0001	3.49 (2.75–4.43)	< 0.0001	3.28 (2.03–5.31)	< 0.0001
Ref: 2000–2003						
2004–2007	0.9 (0.81–0.99)	0.0386	0.92 (0.82–1.03)	0.1353	0.86 (0.69–1.06)	0.1641
2008–2014	0.83 (0.75–0.91)	< 0.0001	0.86 (0.77–0.96)	0.0054	0.74 (0.61–0.9)	0.0031
Analysis of Interaction (multiplicative scale, HR)						
Ref.: surgery in 2000–2003	1					
Period (2004–2007) × neither treatment vs. surgery	0.99 (0.76–1.28)	0.9335	0.98 (0.73–1.32)	0.8949	1.08 (0.63–1.84)	0.7807
Period (2004–2007) × RT vs. surgery	0.9 (0.68–1.2)	0.48	0.83 (0.6–1.14)	0.25	1.41 (0.74–2.68)	0.2916
Period (2008–2014) × neither treatment vs. surgery	1.09 (0.88–1.35)	0.4292	1 (0.78–1.28)	0.9978	1.46 (0.94–2.29)	0.0956
Period (2008–2014) × RT vs. surgery	0.74 (0.58–0.94)	0.012	0.7 (0.54–0.91)	0.0083	0.9 (0.53–1.53)	0.7061
Analysis of interaction (additive scale, RERI)						
Ref.: surgery in 2000–2003	1		1		1	
Period (2004–2007) × neither treatment vs. surgery	− 0.22 (− 0.65, 0.22)	0.32	− 0.23 (− 0.76, 0.31)	0.40	− 0.02 (− 0.72, 0.66)	0.94
Period (2004–2007) × RT vs. surgery	− 0.56 (− 1.17, 0.06)	0.07	− 0.76 (− 1.47, − 0.05)	0.03	0.83 (− 0.31, 2.0)	0.14
Period (2008–2014) × neither treatment vs. surgery	− 0.11 (− 0.51, 0.29)	0.57	− 0.29 (− 0.80, 0.22)	0.25	0.45 (− 0.08, 0.99)	0.09
Period (2008–2014) × RT vs. surgery	− 1.18 (− 1.80, − 0.55)	0.0002	− 1.25 (− 2.0, − 0.53)	0.0005	− 0.83 (− 2.07, 0.42)	0.18

Effect estimates refer to hazard ratios with 95% confidence intervals from Cox-regression models. Interaction analyses were performed on a multiplicative and additive scale

HR hazard ratio, *CI* 95% confidence interval, *RERI* risk excess due to interaction

2000–2003. Accordingly, Haasbeek et al. (2012) found an improved survival for the subgroup of patients treated with radiotherapy or surgery in The Netherlands. In contrast, Palma et al. reported a survival improvement to be confined solely to the RT group. In the analysis by Haasbeek et al., survival remained unchanged in the group of untreated patients (Palma et al. 2010; Haasbeek et al. 2012). However, in our analyses, we found an improvement in all groups for the time after 2007, which might be explainable by the consideration of more recent data in our analyses. Extending the work by Palma et al. (2010), our study estimated the treatment effect (surgery vs. radiotherapy) in relation to period directly by computing the statistical interaction and found a strong effect in men who have a lower survival than female lung cancer patients as demonstrated by the previously mentioned population-based survival analysis (Eberle et al. 2015).

In addition, we found an increase in the proportion of cases that were treated by radiotherapy after 2007 when compared to the time before the general introduction of

SBRT in Germany and the transition period (5–6%). These observations stand in line with population cancer registry data from The Netherlands, where also an increase in RT utilization over time was noted along with an increasing availability of SBRT (Palma et al. 2010; Haasbeek et al. 2012).

It needs to be acknowledged that improvements in surgical techniques and increased use of imaging diagnostics such as FDG-PET (fluorodeoxyglucose positron emission tomography) may also have affected both, the surgery and the radiotherapy groups. This together with the more widespread use of SBRT especially in the last period could have fostered a stronger effect related to treatment in the radiotherapy group. The strongest impact of FDG-PET on treatment-related mortality might result from a stage migration to higher stages due to PET imaging (van der Drift et al. 2012; Morgensztern et al. 2008). Such an effect might move subjects with an adverse survival prospect (high FDG-PET uptake) to higher stages and bias survival analyses towards a virtual improvement. At the time of treatment initiation, this effect would not be confined to the radiotherapy group, but should affect surgery and radiotherapy. In addition, a better compliance to cancer treatment might have contributed to a better survival in the most recent period (McCarthy et al. 2008). Furthermore, when we examined stages across periods no decease in the proportion of UICC I cases was present in the data making such stage migration unlikely to be a source of bias.

Most cancer registries used in this study defined the initial treatment as the therapy that was administered within 6 months after the first diagnosis. Thus, in the early years lacking a non-invasive treatment option with high local control, symptomatic patients might have been the primary recipients for radiotherapy. This explains the worse survival prospect in the years before 2008 in the radiotherapy group when compared to cases that received neither radiotherapy nor surgery. In addition, the group with neither radiotherapy nor surgery might contain alternative treatments such as radiofrequency ablation or chemotherapy that might contribute to the slightly better survival of this group in early years. Thus, only with a wide availability of SBRT, radiotherapy became a viable option as an alternative to surgery in certain patients.

As it was mentioned earlier, the larger coverage of incident lung cancer cases in the period after 2007 might result in biased effect estimates if, e.g., age and clinical performance of recorded patients might differ systematically between periods and treatment. As the analysis was adjusted for age considering also non-linear relations and there was no evidence for a change of other considered covariates in terms of mortality prediction between periods, there is no reason to expect biases in the estimation of period effects. However, clinical data such as performance indices (e.g., ECOG) are not available in epidemiological cancer registries. The primary objective of this study was to assess the impact of a wider availability of SBRT in Germany on lung cancer mortality in the population. Thus, a major bias caused by missing individual data is unlikely as long as the population characteristics across treatment groups remain stable over time. Interestingly, there was no evidence for an alteration in the association of other considered covariates with mortality that was modified by the period of treatment.

Furthermore, the use of SBRT was not directly reported in the statistics, as it is the case in most population-based registries (Palma et al. 2010). Still, a minority of patients might thus be treated with normal fractionated radiotherapy. If this was the case, we would expect an underestimation of effect estimates for radiotherapy when compared to surgery and thus a lower power to reveal a period effect. A similar reasoning applies to the fact that some centres might have started with SBRT already between 2000 and 2007.

For the elderly patient population in Germany, a significantly reduced survival was previously reported for 80+-year-old patients compared to < 60-year-old patients (8.4% vs. 18.5% for 5 years) (Eberle et al. 2015). When we focused on the subgroup of elderly patients, that is 75 years and older, a lower risk of death could be determined in the period with wide availability of SBRT (after 2007) compared to the time between 2000 and 2003 with limited availability of SBRT, which, however, applied to both, surgery and radiotherapy, in comparable magnitude.

In a similar way, when the subset of high-quality data was considered we found virtually the same effect size as in the full cohort. This again gives rise to the conclusion that the cohort composition, because of a higher coverage of incident cases in recent years, is unlikely to have affected our findings.

Conclusion

In conclusion, by considering population-based data, we found an improved survival of stage I lung cancer cases in recent years. With an increasing application of radiotherapy related to a wider availability of SBRT, the improvement in survival was strongest in patients treated with radiotherapy. Our findings show that from a public health perspective investments in emerging techniques are necessary and can result in a measurable improvement in terms of survival in a large patient cohort. This is especially true for vulnerable patients that are no candidates for invasive treatments.

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Compliance with ethical standards

Conflict of interest The authors have declared no conflicts of interest.

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