Leiden University Medical Center

Netherlands comprehensive cancer organisation

FPN: 181P

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Ninety-day mortality following curative intent radiotherapy for stage I-III lung cancer in the Netherlands

Introduction

To improve treatment quality and thereby reduce the outcome variability, various national and international cancer care organisations developed sets of quality indicators for the treatment of lung cancer. The 90-day mortality is an often included outcome indicator. The existing literature on 90-day mortality presents challenges due to the utilization of diverse selection criteria and definitions. The validity of the 90-day mortality rate for quality monitoring of radiotherapy can be questioned, because early death following radiotherapy for lung cancer is often related to disease progression or (less often) comorbid disease.
In our study we aimed to describe the early mortality after curative radiotherapy for lung cancer in the Dutch lung cancer population. The association between facility volume and 90-day mortality rate was assessed, and the predictive impact of several case-mix and selection criteria were determined. Definitions of 30-day and 90-day mortality were compared.

Patients and methods

This was a retrospective, non-interventional, population-based study using data from the Netherlands National Cancer Registry (NNCR), including adult patients diagnosed with clinical stage I-III lung cancer and treated with curative intent radiotherapy (i.e. SBRT, conventional or hypofractionated radiotherapy), with or without the addition of chemotherapy. From a primary selection of 20,274 patients, we excluded patients treated abroad (n=15), age <19 years (n=34), patients with unknown starting date of radiotherapy (n=160), chemoradiotherapy for stage I-II (n=796) or palliative radiotherapy for stage III (n=914), leaving a final study base of 18,355 patients.
The primary outcome is the 90-day mortality, defined as death <90 days from the start of radiotherapy. As alternative outcomes, we compared death <90 or <30 days from the start or end of radiotherapy. Patients were stratified for age at diagnosis, cTNM stage, treatment period, ECOG performance status and tumor location (upper/middle/lower lobe). To evaluate the impact of facility volume, treatment information was combined within three 6-facility strata (small, medium, large) based on the treatment volume within the 18 Dutch radiotherapy institutions.
The association between clinical characteristics and 90-day mortality was evaluated with multivariable logistic regression analysis. For parameters significantly improving the fit of the model ($p<0.05$), results are reported as odds ratios (ORs) with 95% confidence intervals (CI). P-values for univariable comparisons are not reported, because even small differences become statistically significant with a sizable series.

		Patients no. (%)	90DM(%)	Adj. OR (95% CI)
Age	18-59 60-69 70-79 80+	874 (8.7) 2629 (26.0) 4396 (43.5) 2209 (21.9)	0.92 1.60 2.98 3.53	Ref 1.6 (0.7-3.4) 2.7 (1.3-5.5) 2.9 (1.4-6.0)
Sex	Male Female	5509 (54.5) 4599 (45.5)	3.09 1.94	Ref 0.7 (0.5-0.9)
Period	2015-2016 2017-2018 2019-2020	3034 (30.0) 3392 (33.6) 3682 (36.4)	2.60 2.33 2.74	NS
ECOG PS	0 1 2+ Unknown	2169 (21.5) 3362 (33.3) 1422 (14.1) 3155 (31.2)	1.34 2.56 5.20 2.22	Ref 1.8 (1.2-2.7) 3.7 (2.4-5.7) 1.7 (1.1-2.6)
Tumor location	Central Upper Middle Lower	276 (2.7) 6217 (61.5) 442 (4.4) 3173 (31.4)	3.62 2.14 2.49 3.31	NS
Stage	I II	8555 (84.6) 1553 (15.4)	2.03 5.47	Ref 1.9 (1.4-2.5)
Previous malignancy	No Yes	7138 (70.6) 2970 (29.4)	2.44 2.86	Ref 1.4 (1.1-1.9)
Histology	Adeno Squamous Large other SCLC Clinical	2298 (22.7) 1649 (16.3) 621 (6.1) 79 (0.8) 5461 (54.0)	2.31 3.34 3.06 5.06 2.34	NS
Treatment	SBRT Other	8356 (82.7%) 1752 (17.3%)	2.00 5.25	0.5 (0.4-0.7) Ref
Facility volume	Small Medium Large	1665 (16.5%) 3338 (33.0%) 5105 (50.5%)	2.88 2.70 2.37	NS

Table 1 (left). Patient characteristics, 90-day mortality (90DM) after start of radiotherapy and results of multivariable logistic regression analysis for patients with stage I-II lung cancer (n=10,108).

Results

The study base comprised a total of 18,355 patients with lung cancer, 10,108 with stages I-II and 8,247 with stage III at the time of diagnosis. The 90-day mortality was **2.56%** for patients with stages I-II lung cancer and **4.60%** for stage III.
For stages I-II, age, sex, ECOG performance status, stage, prevalence of previous malignancy and type of radiotherapy were affirmed as predicting factors [Table 1]. The 90-day mortality decreased with increasing facility volume from 2.88% to 2.37%, but the differences were not statistically significant after controlling for case-mix. In 54% of the cases, no pathology diagnosis was obtained. Previous malignancy was common (29%) and the most prevailing treatment procedure was SBRT (83%). The 90-day mortality was lower after SBRT than after other procedures, 2.00% versus 5.25% (OR 0.5 (95%CI 0.4-0.7)), respectively.
For stage III, age, sex, treatment period, ECOG performance status, histology and type of treatment were affirmed as predicting factors [Table 2]. The 90-day mortality was similar for the three facility volume strata and decreased with time from 5.26% in 2015-2016 to 3.73% in 2019-2020 (OR 0.7 (95% CI 0.5-0.9)). Mortality was higher after sequential CRT than after concurrent CRT, 5.93% versus 3.40% (OR 1.5 (95% CI 1.2-1.9)), respectively.
The 30-day mortality rate was considerably lower than the 90-day mortality rate, i.e. 0.62% for stages I-II versus 0.74% for stage 3 [Table 3]. For stage III, 90-day mortality rates calculated from the end of radiation were considerably higher than when calculated from start of treatment, 6.70% versus 4.60% calculated from the end of RT.

		Patients no (%)	90-DM (%)	Adj. OR (95% CI)
Age	18-59 60-69 70-79 80+	1850 (22.4) 3093 (37.5) 2738 (33.2) 566 (6.9)	2.81 4.11 5.33 9.54	Ref 1.3 (1.0-1.9) 1.6 (1.1-2.2) 2.6 (1.7-3.9)
Sex	Male Female	4512 (54.7) 3735 (45.3)	5.72 3.24	Ref 0.6 (0.5-0.7)
Period	2015-2016 2017-2018 2019-2020	2740 (33.2) 2801 (34.0) 2706 (32.8)	5.26 4.78 3.73	Ref 0.9 (0.7-1.1) 0.7 (0.5-0.9)
ECOG PS	0 1 2+ Unknown	3259 (39.5) 2692 (32.6) 507 (6.2) 1789 (21.7)	3.13 5.28 7.89 5.31	Ref 1.6 (1.2-2.1) 2.3 (1.5-3.4) 1.6 (1.2-2.1)
Tumor location	Central Upper Middle Lower	1475 (17.9) 4565 (55.3) 310 (3.8) 1897 (23.0)	5.63 3.94 3.55 5.54	NS
Previous malignancy	No Yes	7332 (88.9) 915 (11.1)	4.60 4.59	NS
Histology	Adeno Squamous Large other SCLC Clinical	2705 (32.8) 2571 (31.2) 1151 (14.0) 1721 (20.9) 99 (1.2)	3.81 5.95 5.82 3.20 1.01	NS
Treatment	RT-only CRT concurrent CRT sequential	697 (8.5) 4648 (56.4) 2902 (35.2)	7.03 3.40 5.93	1.2 (0.8-1.9) Ref 1.5 (1.2-1.9)
Facility Volume	Small Medium Large	1644 (20.0) 2259 (27.4) 4344 (52.7)	4.62 4.56 4.60	NS

Table 2 (left). Patient characteristics, 90DM after start of radiotherapy and results of multivariable logistic regression analysis for patients with stage III lung cancer (n=8,247).

Table 3 (below). General comparison of various definitions of post-treatment mortality

	Stage I-II		Stage III	
	(%)	95% CI	(%)	95% CI
30-day from start of RT	0.62	0.49-0.80	0.74	0.58-0.95
30-day from end of RT	0.96	0.78-1.17	2.61	2.28-2.98
90-day from start of RT	2.56	2.27-2.89	4.60	4.17-5.07
90-day from end of RT	3.20	2.87-3.56	6.70	6.18-7.26

Interpretation

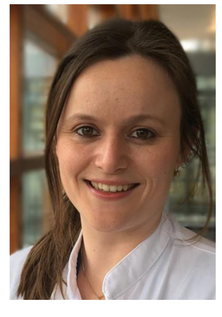
Our study showed that early mortality is correlated with poor prognostic patient and tumor factors. This means that case mix is an important factor to control for when comparing early mortality rates, especially when attempting to draw conclusions regarding the quality of the given treatment. Previous studies (mainly surgical series) have shown that facility volume can be associated with disease outcome: a higher facility volume is thought to be a surrogate measure for treatment experience and state of the art treatment. Facility volume was not associated with 90-day mortality in the current study. Of note is that the Dutch radiotherapy facilities are firmly centralized with a total of 18 facilities each treating a minimum of almost 100 lung cancers per year. As such, Dutch radiotherapy facilities can be considered extremely high volume treatment centers and it is unlikely that a further difference in patient volume will affect disease outcome, especially when the frequency of fatal events is very low. With regard to the 90-day mortality, the low number of events also hampers the ability to detect individual outliers. Nevertheless, if a comparison of 90-day mortality rates is pursued, a uniform definition is recommended. We advise to measure 90-day mortality from the start of radiotherapy, in order for this outcome to be less dependent on the duration of radiotherapy. Furthermore, with a longer time between diagnosis and the event of death, it is more likely that the event is related to disease progression and it will also be more difficult to compare outcomes with results after surgery.

Limitations

One of the main limitations is that absence of certain data may have influenced our primary outcome, (.e.g. cardiac comorbidity, pulmonary function, smoking history, radiation planning, fractionation and dose volume details, cause of death). The risk of selection bias and confounding by indication is also inherent with the use of real-world retrospective data, and it is impossible to account for unknown confounding factors.

Conclusion

Short-term mortality rates following curative intent radiotherapy for lung cancer in the Netherlands are low and independent of facility volume. It was demonstrated that 90-day mortality is an arguable indicator to monitor radiotherapy quality and that standardization of definitions and relevant case-mix factors is warranted.



Conflicts of Interest

The authors declare no conflicts of interest

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