A NTCP model for mortality after chemo-RT for lung cancer including mean heart dose and GTV

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PURPOSE

- Early mortality after (chemo)radiotherapy can be caused by treatment-related toxicities and thus by delivered doses to normal lung and heart.
- Prediction models for early mortality incorporating dosimetry are lacking.
- This study explores the prognostic value of common dosimetric features and constructed a normal tissue complication probability (NTCP) model for mortality.

METHODS AND MATERIALS

- **DATASETS**: Two prospective cohorts of curatively treated stage I-III lung cancer patients were studied
  - Dataset 1: 388 patients treated in 2003-2016
  - Dataset 2: 98 patients treated in 2011-2016 (external validation set)
- Prescribed dose was 66Gy/2Gy (concurrent chemotherapy), 66Gy/2.75Gy (sequential or no chemotherapy) or similar schedules.
- Clinical covariates analyzed: WHO performance status, age, current smoker, T stage, N stage and primary gross tumor volume (GTV) (combining primary tumor and involved lymph nodes).
- Dosimetric covariates analyzed: mean lung dose (MLD) and mean heart dose (MHD)).
- **STATISTICS**: In dataset 1, factors with $p<0.1$ in univariate Cox regression were included in multivariable Cox model building and in logistic regression NTCP model building for the endpoints 6, 12, 18 and 24 months mortality.
- NTCP models were validated in dataset 2 after a refit of model coefficients.

RESULTS

COX REGRESSION RESULTS

- Median follow-up time was 30.8 and 43.3 months in dataset 1 and 2, respectively.
- Multivariable Cox model covariates:
  - MHD (HR=1.026, p<0.001)
  - GTV (HR=1.002, p<0.001)
  - Current smoker (HR=1.39, p=0.03)
  - WHO performance status (HR=1.24, p=0.03)
- Survival curves show an increased mortality associated with higher MHD starting 6 month post RT (Figure 1).

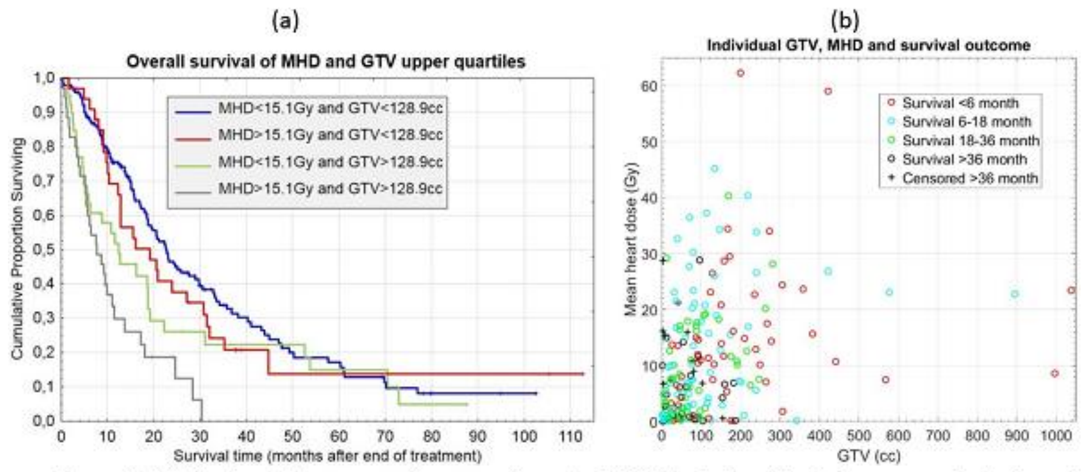

Figure 1 (a) Kaplan-Meier curves for overall survival (OS) in dataset 1. Subgroup analysis based on the upper quartiles of total (primary tumor + lymph nodes) GTV volume (>128.9 cc) and physical MHD (>15.1 Gy). The worst survival was observed for high MHD associated to large GTV (grey curve) with a 1 year OS of 29.8%, 2 year OS of 18.6% and no survivals longer than 30 months. The best survival was seen in the subgroup of patients with both MHD and GTV outside of the upper quartiles (blue curve) with a 1 year OS of 75.5% and 2 year OS of 46.6%. (b) MHD and GTV for all patients in dataset 1 (excluding censored cases before 36 month). Mortality in the high MHD-small GTV region occurs mostly during the 6 to 18 month timeframe (blue circles).

NTCP MODELING RESULTS

- Mortality model at **6 months** (AUC=0.73) included the covariates: GTV, Age, Current smoker
- Mortality model at **12 months** (AUC=0.71) included the covariates: GTV, MHD
- Mortality model at **18 months** (AUC=0.71) included the covariates: GTV, MHD, WHO performance status, Current smoker
- Mortality model at **24 months** (AUC=0.72) included the covariates: GTV, WHO performance status, Age, Current smoker
- MHD was selected in 40%, 100%, 87% and 47% of best performing models (this was only 27%, 47%, 33% and 33% for MLD) at 6, 12, 18 and 24 months.
- The 12 month mortality NTCP model had the highest MHD OR=1.042 (p=0.006) and is depicted in Figure 2.

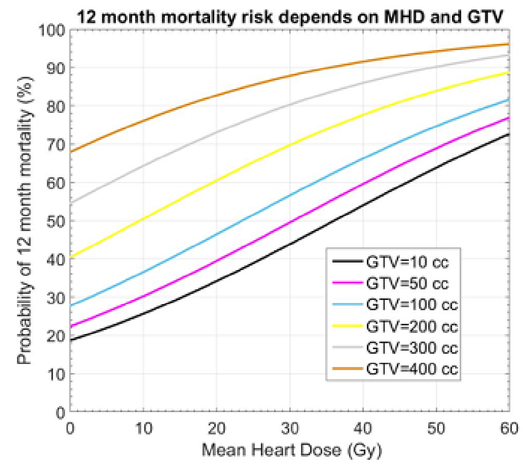

Figure 2 Logistic regression NTCP model for 12 month mortality. MHD dependence (physical dose) of mortality risk for different GTV volumes (primary tumor + lymph nodes). Model calibration was good: Hosmer-Lemeshow p=0.49. Model discrimination was moderate: discrimination slope of 15.6% and AUC of 0.71 (95% CI: 0.63; 0.77). Probabilities can be calculated using $NTCP=(1+e^{-S})^{-1}$ with $S=-1.53+0.041*MHD+0.0057*GTV$.

- In the external validation dataset 2, the 12 and 18 months NTCP models had respective AUCs of 0.60 (0.65 when adding WHO PS) and 0.67. MHD OR was 1.050 (p=0.11) at 12 months.

CONCLUSION

- MHD is a risk factor independent from GTV volume for post RT mortality endpoints later than 6 months and before 18 months.
- A NTCP model for 12 months mortality could allow patient selection for proton therapy.

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