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Oligometastases

Nomogram based overall survival prediction in stereotactic body radiotherapy for oligo-metastatic lung disease ☆,☆☆

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ABSTRACT

Background: Radical local treatment of pulmonary metastases is practiced with increasing frequency due to acknowledgment and better understanding of oligo-metastatic disease. This study aimed to develop a nomogram predicting overall survival (OS) after stereotactic body radiotherapy (SBRT) for pulmonary metastases.

Patients and methods: A multi-institutional database of 670 patients treated with SBRT for pulmonary metastases was used as training cohort. Cox regression analysis with bidirectional variable elimination was performed to identify factors to be included into the nomogram model to predict 2-year OS. The calibration rate of the nomogram was assessed by plotting the actual Kaplan–Meier 2-year OS against the nomogram predicted survival. The nomogram was externally validated using two separate monocentric databases of 145 and 92 patients treated with SBRT for pulmonary metastases.

Results: The median follow up of the trainings cohort was 14.3 months, the 2-year and 5-year OS was 52.6% and 23.7%, respectively. Karnofsky performance index, type of the primary tumor, control of the primary tumor, maximum diameter of the largest treated metastasis and number of metastases (1 versus >1) were significant prognostic factors in the Cox model (all $p < 0.05$). The calculated concordance-index for the nomogram was 0.73 (concordance indexes of all prognostic factors between 0.54 and 0.6). Based on the nomogram the training cohort was divided into 4 groups and 2-year OS ranged between 24.2% and 76.1% (predicted OS between 30.2% and 78.4%). The nomogram discriminated between risk groups in the two validation cohorts (concordance index 0.68 and 0.67).

Conclusions: A nomogram for prediction of OS after SBRT for pulmonary metastases was generated and externally validated. This tool might be helpful for interdisciplinary discussion and evaluation of local

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and systemic treatment options in the oligo-metastatic setting.
Key message: A nomogram for prediction of overall survival after stereotactic body radiotherapy (SBRT) for pulmonary metastases was developed and externally validated. This tool might be helpful for interdisciplinary discussion and evaluation of local and systemic treatment options in the oligo-metastatic setting.

Traditionally, metastatic disease has been considered incurable, with surgery and radiotherapy only performed in palliative intent. In 1995, Hellman and Weichselbaum introduced the concept of " oligo-metastasis", which is defined as an intermediate stage between loco-regional disease and widespread systemic disease [1]. In such selected patients with metastases limited in number, size and involved organs, local treatment, most frequently surgical resection, has resulted in better-than-expected overall survival (OS) [2]. Whereas the efficacy of surgical resection has not been proven in randomized controlled trials, the CLOCC study reported improved long-term OS after radiofrequency ablation with chemotherapy of unresectable colorectal liver metastases compared to chemotherapy alone [3]. Recently, a randomized phase II trial reported substantially improved progression-free survival if local consolidative therapy (mostly some form of radiotherapy) was added to standard systemic treatment in patients with oligo-metastatic non-small cell lung cancer (NSCLC) [4].

The goal of local intervention in oligo-metastatic disease is to locally eradicate all oligo-metastatic lesions aiming at prevention of organ destruction or further systemic dissemination originating from the oligometastatic lesions. Conventional radiotherapy has not been practiced frequently in this setting because treatment required several weeks and local metastasis control remained poor due to low irradiation doses. This has changed with the availability of advanced treatment planning and accurate treatment delivery of stereotactic body radiotherapy (SBRT) [5,6], which is today the treatment of choice for medically inoperable patients with stage I NSCLC [7,8]. These results have prompted the evaluation of SBRT in the oligo-metastatic setting and several prospective phase I/II trials reported highly promising and consistent results in terms of local tumor control and excellent toxicity profile [9–12]. However, OS varied substantially and despite treatment for oligo-metastatic disease, the majority of the patients suffered from systemic progression of disease. In the era of precision medicine, patient selection criteria for or against the use of SBRT are therefore eagerly needed to minimize over- and under-treatment.

Despite the uncertainties concerning patient selection criteria, SBRT for oligo-metastatic disease is becoming routine clinical practice outside of clinical trials. A recent survey among 30 SBRT institutions from 6 European countries reported that 90% were practicing SBRT for pulmonary metastases in 2012 [13]. Another survey among >1000 radiation oncologists in 43 countries showed that 61% of all responders were practicing SBRT for patients with maximum 3 oligo-metastatic lesions and the lung was the most common organ treated [14].

This discrepancy between rapid adoption of SBRT for oligo-metastatic disease despite the lack of established patient selection criteria for or against the use of SBRT was the rationale for this analysis. Consequently, it was the aim to establish a nomogram predicting OS after SBRT for pulmonary metastases.

Materials and methods

In 2012 the working group Stereotactic Radiotherapy of the German Society for Radiotherapy and Oncology (DEGRO) invited all German radiotherapy centers to contribute to a pooled database of patients treated with SBRT for lung metastases. Participating centers were required to have experience in SBRT beyond the implementation phase: a minimum of 20 patients had to be treated with SBRT until 2012. The study was approved by the Ethics committee of the University Hospital Heidelberg (S-280/2014).

Patients treated with SBRT for pulmonary metastases from all types of primary tumors were included into this study: patients were medically inoperable, suffered from unresectable pulmonary metastases or refused surgical resection. All centers used risk-adapted fractionation schemes, the number of SBRT fractions and single-fraction doses were adjusted to tumor size and tumor location (peripheral vs. central). The centers reported patient, tumor, treatment characteristics and outcome data in an anonymized electronic file and sent it to the coordinating center, which established a pooled database. The final database was supported by 20 centers, which are located in Germany ($n = 19$) and Switzerland ($n = 1$) and all except for three are academic university hospitals.

The following clinical parameters were investigated regarding their prognostic impact on OS: age, gender, Karnofsky performance index (KPI), primary tumor site, local control of the primary tumor, treatment intent of the primary tumor (curative vs. palliative), time interval between primary diagnosis and SBRT of the metastases, maximum diameter of the largest treated lung metastases, number of additional metastases (not limited to pulmonary metastases), their location (cranial, extra-cranial or both) and their local control and previous chemotherapy (Table 2).

Modeling, calibration and internal validation of the nomogram

Kaplan–Meier curves were generated to estimate OS, which was defined as the time between the start of SBRT of the first lung metastasis and the death of the patient from any cause. Missing values were imputed using the MICE algorithm, which is a chained equation algorithm in the R software [15]. The Cox proportional hazard model was used for the multivariate analysis of patient survival. To select the significant factors, Akaike's Information criterion (AIC) in combination with bidirectional variable elimination was applied. The final predictor set of this Cox model was used to build the nomogram to estimate 2-year OS.

The nomogram's prognostic accuracy was measured using the bootstrap estimated concordance index. Additionally, the patients were divided into 4 risk groups based on the nomogram. For that the range of total points in the training cohort was divided by four. The prognostic accuracy of these four risk groups was measured using the concordance index.

The calibration rate of the nomogram was assessed by plotting the actual Kaplan–Meier 2-year OS in the four risk groups against the nomogram predicted survival. The analysis was performed using R 3.2.0 Software.

External validation of the nomogram

The nomogram model was externally validated using two independent patient cohorts treated with SBRT for oligo-metastatic lung disease:

(1) 92 patients treated at the Aarhus University Hospital (Aarhus cohort)