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SBRT of lung cancer

Histology of non-small cell lung cancer predicts the response to stereotactic body radiotherapy

Juliane Hörner-Rieber [a,b], Denise Bernhardt [a,b], Julian Dern [a,b], Laila König [a,b], Sebastian Adeberg [a,b], Angela Paul [a,b], Claus Peter Heussel [c,d,e], Jutta Kappes [c,e], Hans Hoffmann [c,g], Felix J.P. Herth [c,f], Jürgen Debus [a,b], Arne Warth [d,h,1], Stefan Rieken [a,b,*,1]

[a] University Hospital Heidelberg, Department of Radiation Oncology; [b] National Center for Radiation Oncology (NCRO), Heidelberg Institute for Radiation Oncology (HIRO); [c] Translational Research Unit, Thoraxklinik, Heidelberg University, Germany Translational Lung Research Centre Heidelberg (TLRC-H), Member of the German Centre for Lung Research (DZL); [d] Department of Diagnostic and Interventional Radiology, University-Hospital; [e] Department of Diagnostic and Interventional Radiology with Nuclear Medicine, Thoraxklinik at University-Hospital; [f] Department of Pneumology, Thoraxklinik, Heidelberg University; [g] Department of Thoracic Surgery, Thoraxklinik, Heidelberg University; and [h] Institute of Pathology, Heidelberg University, Heidelberg, Germany

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ABSTRACT

Background and purpose: To investigate the prognostic impact of different histological subtypes of non-small cell lung cancer (NSCLC) on outcome following stereotactic body radiotherapy (SBRT) for NSCLC patients.

Materials and methods: We analyzed 126 consecutive patients with early-stage adenocarcinoma or squamous cell carcinoma treated with SBRT from 2004 to 2016. Adenocarcinoma patients were further subclassified as high-risk or low-risk tumors.

Results: With a median follow-up time of 22 months, 2-year overall survival (OS), local (LC), and distant control (DC) were 68%, 90% and 79%, respectively. For LC, histologic subtype was identified as major independent prognostic factor ($p = 0.033$): while LC was 81% for squamous cell carcinoma patients, LC was significantly improved for high-risk and even more non-high-risk adenocarcinoma patients with 96% and 100%, respectively ($p = 0.026$). The negative prognostic impact of the histologic subtype "squamous cell carcinoma" was not evident when patients received SBRT with higher total doses in EQD2 (2 Gy equivalent dose): if patients were treated with a total dose in EQD2 $\geq$ 150 Gy, no significant difference in LC for histologic subtypes was detected anymore ($p = 0.355$).

Conclusion: In the current study, histologic subtypes of NSCLC predicted local control probabilities following SBRT. Prospective, multi-center studies are needed to evaluate the prognostic impact of histology and consecutively the need for SBRT dose adaptation.

Surgery is the standard treatment for fit and operable patients diagnosed with early-stage non-small cell lung cancer (NSCLC) [1,2]. However, up to 20% of patients are classified medically inoperable due to severe cardiopulmonary comorbidities [3,4]. For these patients and those refusing surgery, stereotactic body radiotherapy (SBRT) is the treatment of choice with excellent local control of more than 90% after three years and good survival rates [3,5,6].

Regarding surgical outcomes, several risk factors are known for local recurrence after resection of early-stage NSCLC: limited surgery, positive surgical margins, as well as histologic subtypes among others [7]. Indeed, several larger retrospective surgical series reported that local relapse was significantly higher in early-stage NSCLC patients with squamous cell carcinoma or large cell histology compared to adenocarcinoma patients [7–9]. Furthermore, the current WHO classification differentiates 5 distinct predominant histological adenocarcinoma subtypes: lepidic, papillary, acinar, micropapillary and solid [10]. Surgical studies illustrate that outcome including local recurrence is significantly dependent on these respective histologic subtypes [11–14]. First data even

* Corresponding author at: Department of Radiation Oncology, University Hospital Heidelberg, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany.

E-mail addresses: juliane.hoerner-rieber@med.uni-heidelberg.de (J. Hörner-Rieber), julian.dern@med.uni-heidelberg.de (D. Bernhardt), denise.bernhardt@med.uni-heidelberg.de (J. Dern), laila.koenig@med.uni-heidelberg.de (L. König), sebastian.adeberg@med.uni-heidelberg.de (S. Adeberg), angela.paul@med.uni-heidelberg.de (A. Paul), clauspeter.heussel@med.uni-heidelberg.de (C.P. Heussel), jutta.kappes@med.uni-heidelberg.de (J. Kappes), hans.hoffmann@med.uni-heidelberg.de (H. Hoffmann), felix.herth@med.uni-heidelberg.de (F.J.P. Herth), juergen.debus@med.uni-heidelberg.de (J. Debus), arne.warth@med.uni-heidelberg.de (A. Warth), stefan.rieken@med.uni-heidelberg.de (S. Rieken).

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demonstrated a significant predictive effect for adjuvant treatment [13,15]. Especially micropapillary and solid adenocarcinomas are known to be associated with significantly higher risks for progressive disease and worse outcome [11,12,14,16,17].

Interestingly, up to now, most studies on SBRT for early-stage NSCLC did not investigate histology as a possible risk factor or did not detect a significant influence of histologic subtype on outcome [18–23]. Hence, different histologic subtypes are not routinely relevant for treatment-related decisions on irradiation dose and applied fractionation schemes in pulmonary SBRT [3,24,25]. However, two currently published reports supposed that local control following SBRT might also be highly dependent on histologic subtype [26,27]. Therefore, this study now aims to further clarify the prognostic impact of different NSCLC subtypes on efficacy of SBRT and its possible treatment-related consequences.

Materials and methods

Patient population

One-hundred-and-twenty-six consecutive patients were identified from our institutional database with biopsy-proven stage I to IIb (stage T1-T3 N0 M0) (8th edition of the TNM classification) adenocarcinoma or squamous cell carcinoma who received SBRT between January 2004 and October 2016. After staging and cardiopulmonary functional assessment, all patients were classified medically inoperable by an interdisciplinary tumorboard (thoracic surgeon, pulmonologist, oncologist, radiation therapist, and radiologist).

Staging with a computed tomography (CT) scan of the chest was performed for all patients, patients received further diagnostic imaging including fluordesoxyglucose positron emission tomography (FDG-PET) and cranial magnetic resonance imaging when clinically indicated. Additionally, baseline pulmonary function testing was obtained from each patient. The analysis was approved by the Ethics committee of the University Hospital Heidelberg (S-140/2016).

Radiation therapy

Detailed patient selection, imaging protocols, and treatment techniques have been described previously [28–32]. Risk-adapted fractionation schemes were applied, which meant that dose and fractionation schemes were adjusted to tumor size and location (peripheral vs. central), but not histology. Tumors were classified to be "peripheral" or "central" according to the RTOG definition [33,34]. Until 2011, pulmonary SBRT was performed with a single fraction of 24–30 Gray (Gy) prescribed to the 90–95% isodose line, depending on proximity to critical structures ($n = 33$). Afterward, peripheral lesions were treated with three fractions of 15–18 Gy, prescribed to the conformally enclosing 65% isodose line ($n = 48$), while central lesions were irradiated with eight fractions of 7.5 Gy prescribed to the 80% isodose line ($n = 39$). Six lesions in close proximity to the stomach were irradiated with 10 fractions of 5 Gy ($n = 6$). Organs at risk (OARs) and normal tissue constraints were adopted as recently described by the Stereotactic Radiotherapy Working Group of the German Society of Radiation Oncology [3]. Delivery techniques were either 3-D ($n = 91$), helical tomotherapy ($n = 24$), or volumetric-modulated arc therapy (VMAT) ($n = 11$).

In order to correlate irradiated doses with clinical results, the 2 Gy equivalent dose as EQD2 as well as the biological effective dose (BED) were determined: an α/β ratio of 10 Gy was assumed for the tumor. EQD2 and BED were calculated using the linear-quadratic model [35]:

$$\mathrm{EQD2(Gy)} = \text{fractional dose} \times \text{number of fractions} \times \frac{\text{fractional dose} + \alpha/\beta}{2\ \mathrm{Gy} + \alpha/\beta}$$

$$\mathrm{BED\ (Gy)} = \text{fractional dose} \times \text{number of fractions}\left(1 + \frac{\text{fractional dose}}{\alpha/\beta}\right)$$

In detail, median dose in EQD2 at PTV periphery (minimum dose enclosing the PTV) was 93.8 Gy (range 58.7–126.0 Gy) for all patients, while median dose at PTV isocenter (maximum dose) was 121.1 Gy (65.2–261.0 Gy). Patients were in median treated with a single dose of 15 Gy (5–30 Gy) in 3 fractions (1–10 fractions) (Table 1).

Follow-up and outcome evaluation

Routine follow-up visits included a contrast-enhanced CT scan of the thorax after 3, 6 and 12 month intervals following SBRT. If no tumor recurrence was identified in the CT scan after 12 months, CTs and chest X-ray were performed alternately every 6–12 months thereafter. Local progression was classified as progression of the tumor within the high-dose volume. As differentiation between local progression and benign fibrosis in the high-dose volume is known to be challenging, FDG-PET–CT scans or biopsies were applied to distinguish between benign lesions and tumor recurrence. If local progression was suspected, patients were discussed in our institution's interdisciplinary tumor conference (experienced radiologist, radiation therapist, thoracic surgeon, pulmonologist and oncologist) and further procedure was decided. In detail, local recurrence was diagnosed in 12 patients. Of those 12 patients, seven received re-biopsy confirmation of local relapse and three out of the seven additional PET–CT staging. Two patients did not have re-biopsy or PET–CT scan due to simultaneously diagnosed distant progression with multiple metastases. The remaining three patients had severe comorbidities including dementia in all three patients and were therefore only subjected to best supportive care without additional PET–CT scan or biopsy confirmation.

Histologic subtyping

An experienced pulmonary pathologist (AW) classified all biopsy specimens in analogy to the WHO classification system recommendations for surgically resected tumors [10]. All biopsy specimens were centrally reviewed by AW to assure that only adenocarcinoma and squamous cell carcinoma samples were included in the study. For adenocarcinomas the percentage of all growth patterns were recorded and the respective tumors were diagnosed according to the predominant pattern. All specimens were formalin fixed and stained with hematoxylin and eosin and mucin stains (PAS). Mostly, diagnosis of adenocarcinoma or squamous cell carcinoma was achieved solely on the basis of morphologic criteria. In poorly differentiated or solid tumors, immunohistochemical staining against TTF-1, Napsin, p40, and CK5/6 was additionally performed using an automated staining device (Ventana Benchmark Ultra) in an accredited setting. Final diagnoses were made according to the 2015 WHO Classification algorithm for biopsies. For differentiating between high-risk and low-risk adenocarcinoma subtypes, we used the following system based on previously published cohorts [13,36–39].

Low risk: predominant lepidic, acinar, and papillary (type 1 and type 2)
High risk: predominant papillary (type 3), cribriform, solid, and micropapillary

Statistical analysis

Overall survival (OS), local (LC) and distant control (DC) were estimated using the Kaplan–Meier method. Survival curves were