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Original article

Stereotactic ablative radiotherapy after concomitant chemoradiotherapy in non-small cell lung cancer: A TITE-CRM phase 1 trial

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ABSTRACT

Background and purpose: Platinum based chemoradiotherapy is the standard of care for inoperable non-small cell lung cancer (NSCLC). With evidence that NSCLC can have a dose dependent response with stereotactic ablative radiotherapy (SABR), we hypothesize that a SABR boost on residual tumor treated with chemoradiotherapy could increase treatment efficacy. The purpose of this study was to determine feasibility of such an approach.

Material and methods: A prospective phase I trial was performed including 26 patients. Time-to-event continual reassessment method (TITE-CRM) was used for dose escalation which ranged from 3×7 to 3×12 Gy for the stereotactic boost, after 46 Gy (2 Gy per day) of chemoradiotherapy.

Results: Median follow-up was of 37.1 months (1.7–60.7), and 3, 4, 3, 3, 9 and 4 patients were included at the dose levels 1, 2, 3, 4, 5 and 6, respectively. During chemoradiotherapy, 9 patients experienced grade 3 toxicity. After stereotactic radiotherapy, 1 patient experienced an esophageal fistula (with local relapse) at the 3×11 Gy level, and 1 patient died from hemoptysis at the 3×12 Gy level. The 2-year rate of local control, locoregional free survival, metastasis-free survival, and overall survival was 70.3%, 55.5%, 44.5% and 50.8%, respectively.

Conclusion: In the treatment of NSCLC with chemoradiotherapy followed by a stereotactic boost, the safe recommended dose in our protocol was a boost dose of 3×11 Gy.

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Approximately one third of patients with non-small cell lung cancer (NSCLC) will be diagnosed with stage III disease, which is largely inoperable [1]. In patients with good Eastern Cooperative Group Performance Status, the standard of care for inoperable disease consists of a platinum-based chemotherapy doublet with concomitant radiotherapy, with a radiation dose between 60 and 66 Gy in 1.8–2 Gy daily fractions [2–5]. The 2-year Overall Survival (OS) and Progression-Free Survival (PFS) with this strategy are approximately 45% and 30%, respectively [2,6].

Several studies have reported a dose response when treating lung tumors with stereotactic ablative radiotherapy (SABR), with long term local control of >90% when treating with a biological effective dose (BED) $\geq$100 Gy [7,8]. RTOG 0617 was a prospective 2×2 randomized trial evaluating whether dose escalation (74 Gy vs. 60 Gy) and/or the addition of cetuximab would impact OS in stage III NSCLC [2]. This trial showed a surprisingly significant OS detriment in the experimental arm (median OS: 20.3 months vs 28.7 months, $p = 0.004$), which was attributed to an increase in lung cancer related death. By delivering high dose to the tumor with more precise techniques, such as SABR, we could approach a BED of 100 Gy, which may increase the probability of tumor control. However, the safety of a SABR based boost for the treatment of NSCLC has yet to be demonstrated long-term.

The present phase I trial (called CYBERTAXCIS) aimed at testing the feasibility of treating NSCLC with concomitant platinum-based chemoradiotherapy followed by a SABR boost on the residual tumor after conventional radiotherapy.

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Materials and methods

Patients

The trial was registered on December 10th 2008, in the French national registry of trials (ID-RCB number: 2008-A01104-51), and received approval from ethics committees the 4th (AFSSAPS) and 31st (CPP) of December 2008. All patients gave informed consent before inclusion in the trial.

Inclusion criteria were as follows: histologically proven NSCLC; treatment by concomitant platinum based chemoradiotherapy; no previous thoracic irradiation; tumor size less than 5 cm after completing 46 Gy to <4 adjacent targets; Eastern Cooperative Group Performance status (PS) between 0 and 2; no grade 3–4 toxicities according to Common Toxicities for Adverse Events (CTCAE, version 4) 3 weeks after concomitant chemoradiotherapy; deemed as non-surgical candidates after the conventional radiotherapy; ventricular ejection fraction >35%; forced expiratory volume (FEV) >30%; vital capacity >25%; diffusing capacity for carbon monoxide (DLCO) >25%; weight loss< 10%; at least one measurable lesion, adequate hematopoietic, renal and liver function.

Twenty-six patients were treated from 2 different centers (Centre Antoine-Lacassagne, Nice, France, and Hôpital de la Croix-Rouge française, Toulon, France) between April 2010 and August 2015. Clinical work-up at inclusion included: thoraco-abdomino-pelvic (TAP) CT-scan, 18-FDG PET-scan, and brain imaging (either CT-scan or Magnetic Resonance Imaging (MRI)). Follow-up was performed at months 1, 3, 6, 9, and 12 after SABR and then every 4 months thereafter. Follow-up consisted of clinical exam, QLQ-C30 questionnaire and CT TAP scan. If there was suspicion for tumor relapse then 18-FDG PET-scan was performed, with confirmatory biopsy via lung fibroscopy (endobronchial ultrasound: EBUS), or CT guided biopsy when EBUS was not possible.

Treatment procedure

Chemotherapy

Treatment began with 2 induction cycles of docetaxel 75 mg/m^2 (1-h infusion) followed by cisplatin 75 mg/m^2 (30 min infusion) on days 1 and 22. Concomitant chemoradiotherapy (CRT) started on day 43 and consisted of weekly administration of docetaxel 20 mg/m^2 (1-h infusion) followed by cisplatin (20 mg/m^2) for 5 weeks [9]. If patients were at risk of toxicities due to cisplatin and/or docetaxel administration, these drugs were replaced by a carboplatin–paclitaxel regimen (induction: paclitaxel 200 mg/m^2 plus carboplatin area under curve [AUC] 6 on days 1 and 22; CRT: weekly paclitaxel 45 mg/m^2 and carboplatin AUC 2) [2].

Three dimensional conformal radiotherapy

Radiotherapy began on day 43 with concomitant chemotherapy. CT simulation was first performed and treatment planning was calculated for three-dimensional conformal radiotherapy (3DCRT). The target dose of 46 Gy was delivered with an involved field irradiation technique. Treatment was given in 23 fractions, one fraction per day, 5 fractions per week, with 6–18 MV photons utilized (delivered by CLINAC 2100 linear accelerator from Varian©). Daily kV X-rays were used for set-up verification. The gross tumor volume (GTV) included the initial tumor volume and involved nodes (with one of these characteristics: the shortest diameter >1 cm, positive biopsy, or positive 18-FDG PET-avidity at initial evaluation; no additional 18-FDG PET-scan was performed during treatment. The clinical target volume (CTV) was defined as the GTV plus a 3-D expansion of 0.8–1.1 cm. The planning target volume (PTV) was defined as the CTV plus a 1–1.5 cm expansion. The centers participating in this trial used the same margin for CTV and PTV delineation. Dose constraints similar to QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) were used [10].

Stereotactic radiotherapy

Details of SABR treatment methods have been previously described [11]. The Cyberknife© (Accuray, Sunnyvale, United States of America) technology was used for the stereotactic treatment. Twenty-three patients received fiducial implants (two patients received fiducials for two targets and 21 patients were treated for one target), which were tracked by the MTS Synchrony© device [12]. Fiducials were placed between 3DCRT and SABR. After fiducial placement, a new planning-CT (without 18-FDG PET) was performed for the SABR boost treatment plan. Three patients were treated according to tumor density tracking (Xsight Lung©) [13]. Algorithm calculations were performed via Ray Tracing. GTV was the residual tumor on CT-scan. There was no GTV to CTV expansion, and the CTV to PTV margin was 1 mm for upper lung tumors and 2 mm for lower lung tumors. Stereotactic treatment was scheduled 2–4 weeks after the end of CRT. Dose levels 1, 2, 3, 4, 5 and 6 corresponded to 3 consecutive fractions of 7, 8, 9, 10, 11 and 12 Gy, respectively. Dose constraints reported by the AAPM Task Group 101 were used for SABR treatment (except for spinal cord for which maximal dose could not exceed 15 Gy) [14]. Dose constraints were applied on organ at risk minus GTV. Median prescription isodose for SABR was 80% (77–82) and median number of beams used in SABR treatments were 148 (96–251).

Statistical methods

Local control (LC), metastasis free survival (MFS), locoregional free survival (LRFS), and OS were estimated via the Kaplan–Meier analysis. LC was calculated from the last day of SABR until evidence of local relapse, which was defined as a recurrence within the radiated field. Locoregional free survival was calculated from the last day of SABR until evidence of local relapse and/or regional relapse, which were defined as a recurrence within the radiation field, in the mediastinum, or ipsilateral lung. MFS was calculated from the last day of SABR until the evidence of new distant metastasis. OS was calculated from the last day of SABR until death from any cause. Statistical comparisons were performed using Log-rank test. Statistical significance was achieved if p was <0.05. All statistical analyses were two-sided and performed using Statistical Package for the Social Sciences (SPSS) version 16.0., International Business Machines (IBM)©.

BED was calculated with the following formula: BED = $n \times d$ [1 + $(d/\alpha/\beta)$], where n = number of fractions, d = dose per fraction and α/β = 10 for NSCLC. Cumulative BED was calculated by adding the 46 Gy delivered with conventional radiotherapy + the BED delivered during SABR. Doses reached were compared with other studies in the literature.

BED adjusted to overall treatment time was calculated with the following formula: $BED_t = BED - \log_e 2(T - Tk)/\alpha Tp$ [15], where $\log_e 2 = 0.693$, T = duration of radiotherapy, Tk (time of repopula tion) = 28 days for NSCLC and $\alpha Tp = 0.35 \times 3$ for NSCLC.

Dose-escalation design

Study design was performed according to the time-to-event continual reassessment method (TITE-CRM) [16]. In this study, dose escalation guidelines were as followed: (i) the first dose level was 3 × 7 Gy, (ii) at least 2 patients per dose level have to be treated, (iii) the maximal tolerated dose was set at dose level 3 (3 × 9 Gy) where 33% of limiting toxicities where predicted to occur, (iv) each patient had a "weight" that impacts the decision of the next

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