Introduction: To present the outcomes of our technique for medically inoperable both primary and second-primary (SPLC) early stages non-small-cell lung cancer and to integrate the possibility of organising pneumonia (OP) within the irradiation field (IF) by the analysis of radiological changes.

Materials and Methods: Retrospective analysis after the one-year (2011-2012) experience in our hospital. Seventeen patients were treated with the same delivery plan using tomotherapy as a total dose of 60 Gy in 5 fractions. Outcomes and toxicities were recorded and, for SPLC, were described separately. A single radiologist reviewed computed tomography scans.

Results: Sixteen patients were included; five primary lung malignancies (31.3%), 10 SPLC (62.5%) and 1 isolated mediastinal metastasis of lung cancer (6.2%). A pathological proof was obtained for 72.2% of all lesions. The median radiological follow-up was 11.0 (10.5 months for SPLC). For all cases the 6- and 12-months survival rates were 100% and 77.7% (100% and 71.4% for SPLC), and the 6- and 12-months loco-regional control rates counted both for (similarly to SPLC) 100%. Two of 16 patients developed grade 3 late transient (after steroids therapy) radiation pneumonitis and one presented asymptomatic infiltrates as comparable to OP opacities.

Conclusions: The T-SBRT was safe and effective. Mild OP could probably be associated to radiation-induced anomalies into the IF and the knowledge of the possibility of migrating opacities, could help to discern relapse to radiation-induced opacities.

Keywords: Tomotherapy; Stereotactic radiation therapy; Non-small-cell lung cancer; Non-small-cell lung cancer; Organising pneumonia; Radiation pneumonitis

Introduction

Lung cancer remains the first cause of cancer death across the world [1-3]. The curative treatment of early stages primary non-small-cell lung cancer (NSCLC) still requires a surgical resection and, only recently, adjuvant chemotherapy has proved to increase the survival rate in randomised controlled trials (RCT) [4,5]. Owing the fact that, patient’s comorbidities associated to tobacco consumption frequently limit the surgery eligibility [6], the role of the stereotactic body radiation therapy (SBRT) has been rapidly developed as an alternative to surgery with SBRT in patients with operable stage IIB) of medically inoperable lung cancer. The reasons of the SBRT extensive employment result from oncological outcomes comparable to the surgery and limited toxicity. Several prospective studies reporting the use of SBRT for primary stage I NSCLC in patients unfit to undergo surgical resection found a good local control rate (LCR) at 1 (92% [7]), 2 (70% [8]) and 3 years (88% [9]) and the overall survival (OS) was at 1, 2 and 3 years, 84% [7], 65% [8] and between 43% [9] and 56% [10], respectively. If SBRT outcomes for inoperable patients are encouraging, literature regarding those operable is still limited. Lagerwaard et al., reported a prospective database of patients with potentially operable stage I disease treated with SBRT finding a 3-years LCR of 93%, with a 30-day mortality rate of 0% and a 3-years survival rate of 84.7% [11]. As reported by the authors, the predicted 30-day lobectomy mortality in these patients would have been 2.6% according to the thoracoscope predictive model [12]. However, RCT comparing surgery with SBRT in patients with operable stage have not yet been completed and propensity-matched analysis have not found a significant difference concerning both, the OS (1 and 3 years after treatment) between video-assisted thoracotomy lobectomy and SBRT [13], and the early (30-day) morbidity between SBRT (prospective trial RTGO 0236) and sublobar resection (ACOSOG Z4032) [14]. To our knowledge only one study reported oncological outcomes concerning patients (n=27) affected from primary early NSCLC irradiated with SBRT delivered with the use of the tomotherapy (T-SBRT) [8].
Second-primary lung cancer (SPLC) are arbitrary divided into synchronous (SSPLC) and metachronous (MSPLC) [15,16], and as reported by Trousse et al., the incidence seems to increase probably in reason of the increasing detection capacity of radiological imaging techniques as computed tomography (CT) scan and positron emission tomography (PET) scan [17]. Only few retrospective studies reported outcomes following the SBRT for early stages SPLC [18-20], and no one employed the tomotherapy.

The first aim of this study is to retrospectively analyse the one-year (2011-2012) experience in our hospital concerning the T-SBRT employment for medical inoperable early-stages both primary NSCLC and SPLC.

If radiation pneumonitis (RP) is a well-known (early and late) complication of NSCLC treated with SBRT which develops in the irradiation field (IF), only one study described toxicities employing the T-SBRT [8]. The organizing pneumonia (OP) was only recently identified as a symptomatic and transient consequence developing outside the IF [21]. Since classical OP developing after the breast irradiation has been proven to usually start in the IF and successively moving outside [22,23], we hypothesise that, in the IF (in association with RP changing) asymptomatic mild OP could be present and could so be suggested by a landmark dynamical advance without necessarily moving on outside the IF. This is the first study trying to integrate the possibility of OP within the IF by analysing imaging (CT scan) dynamic changes of the IF after the T-SBRT.

Material and Methods

Patient selection

We retrospectively analysed the one-year (2011-2012) experience in our hospital (CHUV, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland), concerning the T-SBRT employment in medical inoperable early-stage primary and second-primary NSCLC consequent cases. The TNM classification was attributed according to the International Association for the study of Lung Cancer (IASLC) [24], which reviewed the TNM classification of Mountain [25]. All patients presenting a distant disease (M1) were excluded except in case of a second ipsilateral nodule in a different lobe; this presentation was classified as T4 and if N was <2 as stage IIa by the IASLC and therefore we included these cases in our study. We defined as early stage tumours, lesions classified between Ia and IIIa. All patients have been staged using contrast-enhanced thoracic CT scan and PET-CT scan. All radiological changes were interpreted in a 3D-mode after the deformable fusion of the diagnostic CT scan by the way of the Velocity software. We defined OP as follows: Peri-bronchial-vascular infiltrate and previous adjacent abnormal areas rested abnormal until advance. For “advance” the radiologist intended that, new pulmonary areas were affected by infiltrates, previous adjacent abnormal areas were affected by infiltrates and previous adjacent abnormal areas rested abnormal until the achievement of the maximal extension and then regressed.

Follow-up and radiological changes

All patients with a radiological follow-up during less than 4 months were excluded. Patients were radiological followed-up the first time between 1 and 4 months after the end of SBRT and then every 3-5 months until 2 years. Patients underwent a clinical follow-up at 1, 3, 6 months and 1 year. The radiological follow-up included both non-enhanced and enhanced CT scans. A single radiologist, blinded to the results and well-experienced in chest imaging, reviewed all CT scans. All consecutive CT scans on a minimal 6-months period, showing loco-regional findings suspicious for progressive disease, were confirmed with PET-CT scan. All radiological changes were interpreted in a 3D-mode after the deformable fusion of the irradiation field(s) on the diagnostic CT scan by the way of the Velocity software. We defined OP as follows: Peri-bronchial-vascular opacities dynamically migrating inside and/or outside the IF in symptomatic or asymptomatic patients with no evidence of other specific aetiology. The radiologist discerned “dynamical migration” from “advance”. For “dynamical migration” the radiologist intended that, if new adjacent lung’s areas were affected by infiltrates, previous adjacent abnormal areas of the lung healed. For “advance” the radiologist intended that, new pulmonary areas were affected by infiltrate and previous adjacent abnormal areas rested abnormal until the achievement of the maximal extension and then regressed.

Statistical analysis

The Kaplan-Meier method was employed to calculate cumulative outcomes (locoregional control rate, distant metastasis-free rate and survival rate) at 6 and 12 months after the end of the T-SBRT and results for SPLC were described separately.
Results

Seventeen medical inoperable early stages NSCLC were treated using the T-SBRT and 16 patients were included in the study. One patient not reached the minimal radiological follow-up. Patient characteristics are summarized in Table 1. Five were treated for a primary malignancy (31.3%), 10 for SPLC (62.5%) and 1 for an isolated mediastinal metastasis of the primary lung cancer (6.2%). Eleven patients had a previously lung surgery, the lobectomy was the most employed technique and concerned 9 cases (56%) in the total group and 8 (80%) in the SPLC sub-group of patients. We counted 18 pulmonary lesions in 16 patients. Detailed lesion’s characteristics are resumed in Supplementary Table 4. A pathological proof could not be obtained for 5 lesions (3 had a not-conclusive histo-cytological analysis and for 2 B-EBUS was not performed) that represented the 27.8% of lesions in the total group and the 41.7% in the SPLC subgroup of patients. Two patients presented multiple ipsilateral lesions and both were patients treated for SPLC (Supplementary Table 4, case 4 and 9). Stage I represented the 81.2% of all patients and the 80% of SPLC. No patient was staged as II and 3 patients were staged as IIIa. Four patients presented a concomitant extra-pulmonary malignancy (non-Hodgkin-lymphoma, salivary gland malignant cancer, colon cancer and breast cancer) and all had a histological confirmation of NSCLC. For all consecutive cases the 6- and 12-months survival rates were 100% and 77.7%, the 6- and 12-months loco-regional control rates were both 100%, and the 6- and 12-months distant metastasis-free rate counted for 93.4% and 82.9%. For SPLC, the 6- and 12-months survival rates were both 100% and 77.7%, the 6- and 12-months loco-regional control rates were both 100% and the 6- and 12-months distant metastasis-free rate counted for 100% and 80%. Four patients (25% of all cases) presented a recurrent disease during the period of study, 3 of them were treated for SPLC and the last-one was treated for a primary disease. Two patients developed an isolated local failure and 2 presented a distant failure (pleural carcinomatosis and brain metastasis). We classified the pleural carcinomatosis as a distant failure because the irradiated mass did not increased in volume, but in opposition, showed a decreased volume. Two patients died (12.5% of all patients) and both were treated for SPLC. No deaths occurred in the firsts 6 months after the end of the T-SBRT. One patient expired in reason of a recurrent distant disease (pleural carcinomatosis) and one developed a fatal uro-sepsis. Dose-metrics mean values are summarized in Table 2.

Table 1: Patients characteristics. Legend; SPLC: Second Primary Lung Cancer.

| Gender        | Consecutive cases (16) | SPLC (10) |
|---------------|------------------------|-----------|
| Male          | 12 (75.0%)             | 9 (90%)   |
| Female        | 4 (25.0%)              | 1 (10%)   |
| Mean age (years) | 70                     | 70.5      |
| Previous surgery | 11 (68.8%)             | 10 (100%) |
| lobectomy     | 9 (56.3%)              | 8 (80%)   |
| pneumonectomy | 2 (12.5%)              | 2 (20%)   |
| Histology     | 18                     | 12        |
| adenocarcinoma| 7 (38.9%)              | 5 (41.6%) |
| squamous cell | 6 (33.3%)              | 2 (16.7%) |

Table 2: T-SBRT characteristics. Legend; Gy: Gray, PTV: Planning Target Volume.

| Parameter                                    | Consecutive case (16) |
|----------------------------------------------|-----------------------|
| Total dose (Gy)                              | 60                    |
| Dose/fraction (Gy)                           | 12                    |
| Number of fractions                          | 5                     |
| Mean lung dose (Gy)                          | 5.3 (range 0.3-20.0)  |
| Biologically effective dose with α/β of 10 Gy (Gy) | 132                   |
| Mean PTV volume (cc)                         | 53.2 (range 12.8-203.8)|
| Mean V5 controlateral (%)                    | 21.0 (range 3.0-44.5) |
| Mean V15 ipsilateral (%)                     | 15.5 (range 0.1-40.7) |
| Mean V30 ipsilateral (%)                     | 7.7 (range 0.0-30.5)  |
| Mean duration of SBRT (days)                 | 17.2 (range 10-27)    |
All consecutive cases (16) | SPLC (10)
---|---
Patients with acute dyspnea interfering with DLA | 4 (25%) | 3 (30%)
Patients with acute dyspnea interfering with DLA resulting from RP | 2 (.5%) | 1 (10%)
Acute dyspnea aetiology | 6 | 4
infectious | 3 | 3
RP (grade 3) | 2 | 1
others | 1 | 0
Radiological findings | | |
RP (grade 1) | 5 (31%) | 3 (30%)
organising pneumonia | 1 (6.2%) | 1 (10%)
Radiological follow-up | | |
median (months) | 11.0 | 10.5
mean (months) | 10.8 | 11.6
range (months) | 4-19 | 6-19

Table 3: Toxicities and radiological findings. Legend; DLA: Daily Living Activities, RP: Radiation Pneumonitis, SPLC: Second Primary Lung Cancer.

The median radiological follow-up reached 11.0 months for all consecutive cases and 10.5 months for SPLC. Toxicities and radiological findings after the T-SBRT are shown in Table 3. No grade 2 RP was recorded. Two patients (Supplementary Table 4, case 5 and 7) developed grade 3 late RP (both at 5 months after the end of T-SBRT) and both were treated with a corticosteroids therapy (0.5-1 mg/kg during a 5-6 months period) with subsequent resolution of symptoms and radiological changes. Five patients (31% of all patients) developed asymptomatic infiltrates outside the IF at time of lesion’s maximal extension. Only one asymptomatic patient (Supplementary Table 4, case 9) presented infiltrates that dynamically move on (limited to the IF) as comparable to organising pneumonia (OP) opacities (Figure 2). No major acute or late toxicity, including asthenia, bleeding, dysphagia, oesophagitis and bronchial necrosis, were reported.

**Discussion**

Since lung cancer is closely associated to the tobacco consumption, it is not surprising that the presence of chronic obstructive pulmonary disease (COPD) and cardiac comorbidities are common in NSCLC patients. If cardiac comorbidities should probably not significantly limit the patient’s surgical accessibility [30], the COPD severity status seems to appear as a relevant limiting surgical factor [6]. In our study patients were all smokers and the patient’s ability to tolerate a surgical resection was limited by the assessment of pulmonary reserve and/or a performance status ≤2. The physiological explanation of SBRT good outcomes seems to be caused by the great CD8+ T-cell immune response against the tumour [31]. Concerning SBRT outcomes for inoperable early stage NSCLC resulting from retrospective analysis, Senthi et al. interested to the pattern of failure (diagnosed by the way of CT and PET) and reported that, more often (66%), the recurrence was localized at distance and disease recurrence counted for 18% of patients (n=124) [32]. Verstegen et al., found for early stages primary NSCLC (n=64) a 1-year loco-regional control rate (LRCR) after SBRT of 96.8% and a prevalence of failures of 20% (62% were distance-relapses) [13]. Concerning prospective studies of medically inoperable...
stage I patients, Taremi et al., found a 1-year-LCR and OS of 92% and 84%, respectively [7]. If in rapport to the literature we found both a comparable prevalence of failures (25%), 1-year distant metastasis-free rate (82.9%), 1-year LRCR (100%) and local-regional failures (n=2) were frequent as distant-failures (n=2), some factors influenced our outcomes; the median duration of follow-up play certainly a role. As explained by Verstegen et al. if the median follow-up period is short, it signifies that more patients with a radiological recurrence are still alive, and consequently, the percentage of failure will be elevated [13]. So, the follow-up duration did not probably played in favour to our both LRCR and metastasis-free rate in reason of our lower value (0.9 years) compared to previous studies (1.6 [7], 2.7 [32] and 2.5 years [13]). Both the rate of malignancy confirmation by samplings [7], and the method employed for the diagnosis of local failures, did not played probably a relevant role; similarly to our research, mostly PET-CT scan (only rarely biopsies could be performed) were used to investigate persistent suspicious infiltrates on routinely CT-scan [7,13,32]. Concerning differences in the SBRT delivery schema; a systematic review of literature of NSCLC (56% were early stages), found that the LCR were ≥85% when both the BED10 (calculated using the dose delivered at least 95% of the PTV) was ≥100 Gy and the BED3 ≤210 Gy [33], and in this study, we reached both a BED10 of 132 Gy and a BED3 of 180 Gy for all patients. If the small pool of patients included in this study limit certainly the interpretation of outcomes regarding our total group of patients (n=16), we included 3 patients staged as IIa (18.8% of all cases), which are normally not classified as early stages. To our knowledge only Marcenaro et al., reported oncological outcome for patients (n=27) affected from primary early (Ia-Ib) stages NSCLC treated with SBRT using the tomotherapy (T-SBRT) [8]. Obtaining both 12-months total LCR of 100% and a total recurrence rate of 25% our rates were in the same good range as those reported by these authors (12-months local control rate >95% and total recurrence rate of 33%), with a similar minimal and median duration of the radiological follow-up (6 months vs. our 4 months and 12 months vs. our 11 months, respectively), local failure diagnostic method (based on PET scan findings), rate of malignancy with pathological confirmation (61% of patients vs. our 69%), and BED10 value (100-120 vs. our 132 Gy). If authors did not find (based on the RTOG Toxicity Criteria) acute or late grade ≥2 RP, we recorded 2 cases (12.5%). To our knowledge the frequency after SBRT for NSCLC of early and/or late grade ≥2 RP varies between 0% [8] and 21% [34], and few dosimetric risk factors have been identified using the linear accellerator as delivery system. In 2011 Stauder et al., published a prospective study concerning medical inoperable NSCLC (27% were metastatic lung lesion) treated by the way of SBRT and the prevalence of early grade ≥2 RP (according to CTCAE v.3.0) reached 12.5% (n=10) and authors identified as a significant factor of grade ≥2 RP a planning target volume (PTV) >60 Gy [35]. Takeda et al. identified using multivariate analysis a high V15 as a significant factor between grade 0-1 RP versus grade 2 RP in early primary and solitary metastatic lung tumors [34]. In 2012 Matsu et al. found in patients treated for primary lung cancer with SBRT, a significant increase of grade ≥2 RP for both an high V25 (>44.2%) and PTV (< 37.7 ml) values [36]. Shibamoto et al., found in their prospective study of stage I NSCLC treated with SBRT, a prevalence of early and late grade ≥2 RP (according to CTCAE v.3.0) counting for 13% (n=24) [37]. So our rate of patients with grade ≥2 RP not appears to be greater compared to the literature.

If SPLC seems to increase [17], few studies analysed their outcomes after SBRT and no one employed the tomotherapy [18-20]. Obtaining a 1-year-OS of 71.4%, a 1-year-metastasis free rate of 80.0% and a 1-year local control rate of 100%, our rates were in the same good range as those (91%, 92.3% and 100%, respectively) reported by Haasbeek et al., concerning patients treated with SBRT (n=5) after pneumonectomy for a primary lung malignancy [18]. If authors based the diagnosis of SPLC on both PET-CT scan findings and the tumor board discussion, and a pathological proof concerned only a minority of patients (20%), we achieved a pathological proof for 60% (n=6) of SPLC. Similarly to the authors, which reported 1 patient developing grade ≥2 RP (6.6%), in our study, also 1 patient treated for SPLC developed grade ≥2 RP (10%). In 2012, a retrospectively review, reported SBRT outcomes of 10 patients (with a median follow-up of 15.5 months) and the authors recorded 4 deaths (40%), any grade ≥2 RP and had no evidence of disease recurrence for 83% (n=5) of the living patients [19]. So, having treated a number of SPLC comparable to the limited literature, we could confirm the T-SBRT as a low-risk and effective treatment. Only recently, organising pneumonia (OP) was related to the SBRT. Murai et al. reported 9 patients (8 early stages NSCLC and unique lung metastasis) which developed organising pneumonia (OP) moving on the IF after the SBRT, and 5 of which, needed corticosteroids therapy [21]. Authors identified a previous grade ≥2 RP as significant predictor of OP on multivariate analysis. Previously, the classical association between radiotherapy and OP was related to whole breast irradiation following conserving surgery [23]. In 2009 Kubo et al., reported an OP prevalence after breast irradiation of 2.9% (n=12) and all cases of grade ≥2 RP developed an OP [22]. Murai et al., defined OP as a mixture of pachy and ground-glass opacity developing in the lung volume receiving less than 0.5 Gy in presence of symptoms (general or respiratory) and with no evidence of specific cause [21]. Since, OP developing after the breast irradiation showed that it usually starts in the IF and then moved on outside [23], we hypothesise that asymptomatic mild OP could not necessary move on outside the IF but could dynamical migrating within the IF and so could be differentiated from RP changes. Defining the IF similarly to Murai et al. [21], we not found changes outside the IF, but a patient (6% of all patients) whose infiltrates dynamically moved on within the IF was reported. Already in 2003, Takeda et al., studied serial changes on CT scan after SBRT and reported that a local consolidation appeared in 73% (n=16) of irradiated lesions (limited to the PTV) and, for 6 cases (38%), the movement of opacity was observed; consolidations disappeared in lungs areas previously touched and appeared successively in new areas [38]. Authors interpreted these findings in relation to fibrosis, in relation to both the lesion’s shrinkage and the concurrently presence of traction-bronchiectasis. We recognize that radiological findings within the IF after SBRT are difficult to interpret and that the clinical priority rests to differentiate radiation- induced opacities from a recurrent disease. However, if the association between OP and SBRT outside the IF is demonstrated, we hypothesize that mild asymptomatic OP could be associated to radiation-induced anomalies into the IF, moreover that the association between grade ≥2 RP and OP is reported concerning both the SBRT for lung cancer and the irradiation for breast cancer.

Conclusions

The T-SBRT for both primary and second primary inoperable early stages NSCLC was safe and effective. Probably, mild asymptomatic OP could be associated to radiation-induced anomalies into the IF and the knowledge of the possibility of migrating opacities, could help to discern relapse to radiation-induced opacities.
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