Original Article

CyberKnife® stereotactic radiation therapy for stage I lung cancer and pulmonary oligometastases: is fiducial implantation still relevant?—a cohort study

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Background: Few studies have investigated whether there is a difference in local control or overall survival rates following treatment with robotic stereotactic body radiation therapy (SBRT) with or without prior fiducial marker implantation. Our study aimed to investigate this in patients with primary or secondary lung tumors.

Methods: A retrospective study was conducted at the Institut de Cancérologie de Lorraine of patients treated for primary lung cancer or pulmonary oligometastases with SBRT from January 2013 to July 2016. We included patients at least 18 years old who had stage I non-small cell lung cancer (NSCLC) or lung metastases and a follow-up of at least 1 month.

Results: A total of 294 patients were included. Tumors included 122 lung metastases, 89 stage I NSCLC, and 83 non-histologically confirmed lung lesions. The tracking methods were Synchrony® in 191 cases (119 gold seeds and 72 coils) and Xsight® Spine with 4D computed tomography in 103 cases. Median follow-up was 31.6 months [interquartile range (IQR), 18.1–50.2 months]. The two- and five-year probability of local control were respectively 92.22% [95% confidence interval (CI): 0.89–0.95] and 85.35% (95% CI: 0.79–0.99). The two- and five-year probability of overall survival were respectively 87.46% and 72.77% (P=0.586). Local control rates did not significantly differ between techniques at 2 and 5 years (P=0.685) (gold seeds, coils or Xsight® Spine) within tumors grouped by location, gross tumor volume (GTV) (respectively P=0.9, P=0.7, and P=0.4), planning target volume (PTV) (respectively P=0.4, P=0.9, and P=0.7), or PTV/GTV ratio (respectively P=0.6, P=0.6, and P=0.5). Metastasis-free survival and Overall survival rates did not significantly differ between techniques at 2 and 5 years (P=0.664 and P=0.586, respectively). There were no grade 4 or 5 toxicities and only one grade 3 pneumonitis and one grade 3 pneumothorax.

Conclusions: Fiducial-less SBRT using Xsight® Spine is a safe alternative to Synchrony® using gold seeds or coils, with comparable local control and overall survival rates and a similar toxicity profile.

Keywords: Real-time tracking; fiducial markers; Cyberknife®; stereotactic radiotherapy; lung cancer

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Introduction

Stereotactic body radiation therapy (SBRT) using a conventional linear accelerator (LINAC) or specific machine such as CyberKnife® (Accuray Inc., Sunnyvale, USA) is one of the curative options available for treating unfit patients (ineligible for surgery) with stage I non-small cell lung cancer (NSCLC) (1-6). Local control rates with this technique are around 90–97% at 2–3 years of follow-up with low toxicities (7-12) for peripheral lesions and 87–89% for centrally located lesions (13). SBRT is also a suitable alternative to surgery for lung oligometastases (6,14,15). One of the advantages of the CyberKnife® robotic radiotherapy system is the capacity for real-time tracking of tumors using one of the two methods available: Synchrony®, which uses fiducials such as gold seeds or intravascular coils implanted near the tumor prior to treatment, or Xsight® Lung (Lung Optimized Treatment®), which can directly track the tumors without fiducials. Both of these techniques compensate for respiratory movement (16). A third treatment modality is available: Xsight® Spine (Spine Supine®), which uses the spine as a marker and locates the tumor according to its positional relationship with the spine. Of these three modalities, only Synchrony® requires fiducials to be implanted near the tumor before treatment. After the introduction of these fiducial-less treatment options to the CyberKnife® system, studies comparing the local control rates of Synchrony® with gold seed or coil markers and Xsight® Spine are needed—only a small number of studies have sought to do this to date. Only a few patients have been treated with Xsight® Lung in our center, and so this technique was excluded from this study.

Highlight box

Key findings

- Fiducial-less stereotactic body radiation therapy (SBRT) using Xsight® Spine is a good alternative to Synchrony® using gold seeds or coils when feasible.

What is known and what is new?

- Few studies have investigated whether there is a difference in local control or overall survival rates following treatment with robotic SBRT with or without prior fiducial marker implantation.
- Fiducial-less SBRT using Xsight® Spine is a safe alternative to Synchrony® using gold seeds or coils.

What is the implication, and what should change now?

- Comparable local control and overall survival rates.
- Comparable toxicity profile.

Our study aimed to identify whether there is a difference in local control or overall survival rates for patients with primary or secondary lung tumors treated with SBRT with or without prior fiducial marker implantation, we chose to separate coil and gold seed techniques for homogeneity reasons, in our experience, coils tend to be a little less accurately implemented and far away from the lesions than the gold seeds, it also seems to result in more tracking failure. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1245/rc).

Methods

Patients

We conducted a retrospective analysis of all the patients at the Institut de Cancérologie de Lorraine who underwent CyberKnife® stereotactic radiotherapy for primary lung cancer or lung oligometastases from other cancers between January 2013 and July 2016. Patients' clinical and dosimetric data were retrieved from the hospital's electronic patient files (EPFs). The eligibility criteria for this study were as follows: patients were at least 18 years old, diagnosed with a stage I lung cancer or lung metastases from another cancer, and had a follow-up of at least 1 month. Histologic confirmation was not mandatory, especially in the event that tumors displayed a suspicious appearance on imaging (malignant characteristics), that patients were smokers or former smokers or had a prior lung cancer history, or where there was evidence of lesion growth on follow-up computed tomography (CT) scans and fluorodeoxyglucose (FDG) avidity on positron emission tomography (PET)/CT scans (17). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by regional ethics committee of Lorraine Cancer Institute (registration No. MR0004) and individual consent for this retrospective analysis was waived.

Treatment methods

Depending on the tumor location and the patient's characteristics, one of the following methods was selected:

Synchrony®

This method uses fiducials such as gold seed or coils implanted near the tumor prior to treatment to provide a level of accuracy within 1.5 mm. It is based on the

simultaneous identification of internal and external movements using a combined tracking system composed of an external X-ray system for internal marker localization on kV images and a camera-based system to record movement of the patient chest using LED fixed on a vest. A correlation model is then constructed evaluating the relationship between those movements. Thanks to this correlation model, internal movement can be predicted using external movement and then used to guide to robotic linac to compensate for real time motion. A minimum of four to six fiducials are recommended by the manufacturer, most teams only implant two to three fiducials, its noteworthy that not all the fiducials need to be tracked during treatment. Gold seed implantation is usually performed by a radiologist under CT guidance when the patient's health status and pulmonary function are compatible with the procedure and the risk of a clinically significant pneumothorax is low (18). A one-night hospitalization is required and a chest X-ray excluding major complications is performed before the patient is discharged. In the case of unfit patients for these procedures, such as patients with a WHO performances status ≥2, high Charlson score or incompatible cardiopulmonary function, intravascular markers such as coils are preferred, usually, endovascular embolization coils are placed via the femoral vein into subsegmental pulmonary artery branches near the tumor under biplane angiography guidance (19). An alternative to these procedures is the use of navigational bronchoscopy which result in a lower rate of pneumothorax and the possibility to perform a biopsy during the same procedure if needed (20), however this technique is not widely available at the moment.

Xsight® Spine (Lung Optimized Treatment®)

In this noninvasive method, when tumors are located close to the spine (less than 50 mm from the middle of the posterior wall of the vertebra), the spine can be used as a marker and linked to a 4D scan to obtain an internal target volume (ITV), which compensates for the absence of respiratory movement compensation due to the lack of direct tumor tracking.

Xsight® Lung (Spine Supine®)

Only a few patients have been treated with Xsight® Lung in our center during this period mostly because the majority of our data comes from the early uses of lung SBRT in our institution, Xsight® lung was not as effective as it is now and resulted in a lot of tumor detection failure in the early settings, we chose to use preferentially the other methods available as it also reduced the treatment volumes and the workflow on our simulation scanner.

Treatment planning

All patients were treated at the same institute: the Institut de Cancérologie de Lorraine in Nancy. A free-breathing CT scan without contrast encompassing the entire lung was obtained with millimeter-thick slices for the Synchrony® method the patient block his breathing mid cycle during this scan, without forced inspiration or expiration to avoid motion blur; for Xsight® Spine planning, a 10-phases 4D scan was acquired on a Philips Brilliance Big Bore® CT scanner.

Gross tumor volume (GTV) was delineated by the physicians in the pulmonary window visualization settings. For Synchrony®, this was undertaken on one CT. 2-mm geometric expansion was performed and adapted to anatomic boundaries to obtain the clinical tumor volume. For Xsight® spine, an ITV was obtained after delineating the GTV on the 0%, 30%, 50% and 80% phases of the 4D-scan, merged together as an ITV and then checked on the 4D cinema mode and a subsequent 3-mm (for fiducials closer than 5cm of the spine) to 5-mm (for fiducials further than 5 cm of the spine) expansion was performed to obtain the planning target volume (PTV) depending on the distance between fiducials or spine and the tumor, PTV was not reduced according to organs at risk proximity, however PTV coverage was reduced if needed to respect dose constraints on those structures. All relevant organs at risk (OAR) were delineated, including at least the spinal cord, left and right lung, heart, esophagus, brachial plexus, bronchial tree, and large vessels.

Prescribed doses were 60 Gy in three fractions (21) for peripherally located lesions and 50 Gy in four or five fractions for central or ultra-central tumors (13,22), all delivered to the 80% isodose line.

Follow-up

Patients' toxicities were assessed weekly during treatment, and patients had a follow-up appointment with the radiation oncologist 3 months after treatment completion. Reexamination was then conducted at most once every 3 months. A CT scan was performed at 3 and 6 months and at least annually after this period; in the event of suspicion of recurrence or progression, a PET-CT and biopsy were performed. Local control was evaluated using Response

Evaluation Criteria in Solid Tumors (RECIST) v1.1 (23).

Statistical analysis

Quantitative parameters were described as mean, median, and interquartile range (IQR). The normality of the distribution was assessed by the Kolmogorov test. Qualitative parameters were described as frequency and percentage. Comparisons between the techniques were performed by the Kruskal-Wallis test for quantitative parameters and by the Chi-squared test or Fisher's exact test for qualitative parameters.

Overall survival was defined as death from any cause from the end of radiotherapy to the date of death and metastasis-free survival was defined as death from any cause or metastatic recurrence. These were described with the Kaplan-Meier method. Local control was defined as the absence of progressive disease, which was defined as: local enlargement >20% according to Evaluation Criteria in Solid Tumors v1.1 (23) or confirmed by PET-CT and/or biopsy. It was described as the inverse of the cumulative incidence function to take into account death whatever the cause and metastatic recurrence as competing risks. Late toxicities were described with the cumulative incidence function to take into account death as a competing risk.

Within the subgroup analyses, local control and late toxicities were compared between the techniques with the Gray's test and acute toxicities with the Chi-squared test or Fisher's exact test. Statistical significance was set at 0.05. Statistical analyses were performed with SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 294 patients were treated with CyberKnife® stereotactic radiotherapy at our institute between January 2013 and July 2016 and were included in our study; 294 tumors were treated. A total of 122 were metastases from a distant cancer, 89 were stage I NSCLC, and 83 were not histologically confirmed. Of the 294 tumors, 191 were treated with Synchrony® (119 with gold seeds and 72 with coils) and 103 with Xsight® Spine. 32 patients were excluded for missing data. The median follow-up was 31.6 months (IQR, 18.1–50.2 months).

Tumors characteristics and dosimetric data

Tumor characteristics at baseline are summarized in *Table 1*. Of the 294 tumors treated, 42% were metastases, 30% were stage I NSCLC, and 28% were not histologically confirmed. The most represented primary cancers were lung (47%), unknown (28%), rectal (5%), head and neck (3%), kidney (3%), and colon (3%). Most tumors were located in the upper pulmonary lobes: upper right (37%) and upper left (25%). The median GTV volume was 3.1 cm^3 (IQR, 1.5–7.3 cm^3), the median PTV volume was 19 cm^3 (IQR, 11.2–31 cm^3), and the median PTV/GTV ratio was 5.5 (IQR, 3.8–8.6).

The dosimetric data are summarized in *Table 2*. The fractionation schemes were 60 Gy in three fractions (67%), 50 Gy in four fractions (23%), or 50 Gy in five fractions (7%). The dose constraints for OAR were respected: V20Gy <10% in 94.44% of cases, V10Gy <17% in 86.44% of cases and V5Gy <50% in 99.44% of cases.

Local control, overall survival, and metastasis-free survival

Table 3 summarizes the results for local control, overall survival, and metastasis-free survival. Of the 294 patients treated, 28 experienced local relapses.

Local control at two and five years were respectively

Table 1 Tumor characteristics by technique

Tumor characteristics	All, N=294	Gold seeds, N=119 (40.48%)	Coils, N=72 (24.49%)	Xsight® Spine, N=103 (35.03%)	P value
Lesion type, n (%)					0.003
Metastasis	122 (41.5)	59 (49.58)	24 (33.33)	39 (37.86)	
Primary	89 (30.27)	37 (31.09)	16 (22.22)	36 (34.95)	
Unknown	83 (28.23)	23 (19.33)	32 (44.44)	28 (27.18)	
Total	294	119	72	103	

Table 1 *(continued)*

Table 1 *(continued)*

Tumor characteristics	All, N=294	Gold seeds, N=119 (40.48%)	Coils, N=72 (24.49%)	Xsight® Spine, N=103 (35.03%)	P value
Primary, n (%)					0.04
Lung	137 (46.6)	57 (47.90)	28 (38.89)	52 (50.49)	
Unknown	82 (27.89)	22 (18.49)	33 (45.83)	27 (26.21)	
Others	19 (6.46)	11 (9.24)	2 (2.78)	6 (5.83)	
Rectum	15 (5.10)	9 (7.56)	2 (2.78)	4 (3.88)	
H&N	11 (3.74)	5 (4.20)	2 (2.78)	4 (3.88)	
Kidney	11 (3.74)	5 (4.20)	1 (1.39)	5 (4.85)	
Colon	10 (3.40)	6 (5.04)	3 (4.17)	1 (0.97)	
Sarcoma	9 (3.06)	4 (3.36)	1 (1.39)	4 (3.88)	
Total	294	119	72	103	
Location, n (%)					0.001
Upper right	109 (37.07)	33 (27.73)	27 (37.50)	49 (47.57)	
Upper left	75 (25.51)	32 (26.89)	23 (31.94)	20 (19.42)	
Lower right	48 (16.33)	20 (16.81)	9 (12.50)	19 (18.45)	
Lower left	44 (14.97)	24 (20.17)	5 (6.94)	15 (14.56)	
Middle lobe	18 (6.12)	10 (8.40)	8 (11.11)	0 (0.00)	
Total	294	119	72	103	
PTV margins, n (%)					0.497
2 mm	8 (2.75)	5 (4.20)	1 (1.41)	2 (1.98)	
3 mm	211 (72.51)	89 (74.79)	49 (69.01)	73 (72.28)	
4 mm	48 (16.49)	14 (11.76)	16 (22.54)	18 (17.82)	
5 mm	24 (8.25)	11 (9.24)	5 (7.04)	8 (7.92)	
Total	291	119	71	101	
GTV volume, cm^3					0.785
Mean	5.9	5.7	5.8	6.3	
Median	3.1	2.9	3.9	3.6	
Lower quartile	1.5	1.5	1.4	1.5	
Upper quartile	7.3	7	7.3	8	
PTV volume, cm^3					<0.001
Mean	24.3	20.2	22.6	30.3	
Median	19	15	19	24	
Lower quartile	11.2	9.9	10	15	
Upper quartile	31	26	29.9	42	
PTV/GTV ratio					0.002
Mean	7.3	6	6.4	9.6	
Median	5.5	5	5.2	6.8	
Lower quartile	3.8	3.6	3.6	4.2	
Upper quartile	8.6	7.1	8.3	10.8	

H&N, head and neck; PTV, planning target volume; GTV, gross tumor volume.

Table 2 Dosimetric data by technique

Dosimetric characteristics	All, N=294	Gold seeds, N=119 (40.48%)	Coils, N=72 (24.49%)	Xsight® Spine, N=103 (35.03%)	P value
Dose, n (%)					0.016
60 Gy: 3 fractions	196 (66.67)	88 (73.95)	53 (73.61)	55 (53.40)	
50 Gy: 4 fractions	68 (23.13)	23 (19.33)	11 (15.28)	34 (33.01)	
50 Gy: 5 fractions	21 (7.14)	4 (3.36)	6 (8.33)	11 (10.68)	
Others	9 (3.06)	4 (3.36)	2 (2.78)	3 (2.91)	
Lung V20Gy <10%, n (%)	170 (94.44)	73 (93.59)	42 (100.00)	55 (91.67)	0.177
Median (%) [IQR]	3.3 [0.6–11]				
Lung V10Gy <17%, n (%)	153 (86.44)	67 (87.01)	42 (100.00)	44 (75.86)	0.002
Median (%) [IQR]	8.3 [2–30]				
Lung V5Gy <50%, n (%)	176 (99.44)	77 (100.00)	42 (100.00)	57 (98.28)	NC
Median (%) [IQR]	17.5 [5.1–58.2]				
Lung V5Gy <30%, n (%)	150 (84.75)	68 (88.31)	40 (95.24)	42 (72.41)	0.004
Overall treatment time					0.309
Median days [IQR]	8 [7–11]	8 [7–10]	8 [7–10]	8 [7–11]	

All treatment prescribed to the 80% isodose line. lung V20Gy, lung V10Gy and lung V5Gy: lung volume receiving a dose of 20 Gy, 10 Gy and 5 Gy; IQR, interquartile range.

Table 3 Local control, overall survival, and metastasis-free survival

Survival characteristics	All, N=294	Gold seeds, N=119	Coils, N=72	Xsight® Spine, N=103	P value
Follow-up, months, median (IQR)	31.6 (18.1–50.2)	36.3 (21.3–50.9)	34.7 (22.1–50.7)	26.6 (13–48.6)	NC
Local control, %					0.685
2 years	92.22	93.45	92.24	90.83	
5 years	85.35	87.16	85.56	83.47	
Metastasis-free survival, %					0.664
2 years	82.83	86.15	82.10	79.41	
5 years	55.75	57.85	52.68	55.50	
Overall survival, %					0.586
2 years	84.32	88.89	82.20	80.63	
5 years	59.04	59.81	54.64	61.07	

IQR, interquartile range; NC, not calculated.

92.22% (95% CI: 0.885–0.951) and 85.35% (95% CI: 0.787–0.990) (*Figure 1*). The subgroup analysis (*Table 4*) showed no statistical differences in local control rates between the three modalities for tumor type (primary, metastases or unknown), tumor location (lower, middle or upper lobe, GTV size, PTV size, or PTV/GTV ratio.

Overall survival at two and five years were respectively 84.32% and 59.14% (*Figure 2*). Metastasis-free survival at two and five years were respectively 82.83% and 55.75%. Metastasis-free survival and Overall survival rates did not significantly differ between techniques at 2 and 5 years (P=0.664) and P=0.586, respectively.

Toxicities

Acute and late toxicities are shown in *Table 5*. No grade 4 or 5 toxicities were reported. One acute grade 3 pneumothorax occurred after gold seed implantation; this resolved after surgical management. We reported only two cases of late pneumonitis, one grade 3 in the coil group and one grade 2 in the Xsight® Spine group. Both were radiation induced and resolved after treatment. Pneumothorax and intra-alveolar hemorrhage (IAH) occurred in respectively 36.13% and 7.56% of the gold seed group. Grade ≥2 acute pneumonitis, cough, dyspnea, and asthenia were present respectively in 1.36%, 0.68% 2.16%, and 1.02% of cases. The overall grade ≥2 acute toxicity rate (excluding pneumothorax and IAH) was 5.10%.

Late pneumonitis, cough, dyspnea, and asthenia rates were respectively 0.8%, 0.5%, 5.3%, and 0.4% with an overall grade ≥2 late toxicity rate of 6.1%.

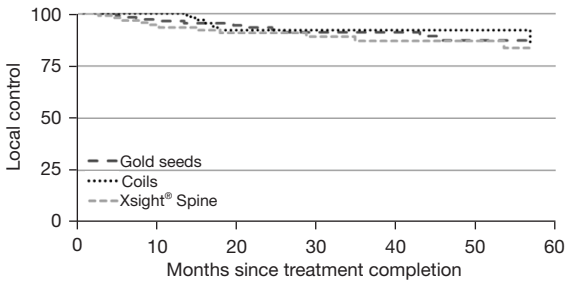

Figure 1 Local control according to the tracking technique used.

Discussion

In our study, the main analysis revealed local control rates

Table 4 Subgroup analysis for five-year local control rate

Characteristics	Relapse/N	Local control, %				
		Total, N=294	Gold seeds, N=119	Coils, N=72	Xsight® Spine, N=103	P value
Tumors						
Primary	12/122	80.65	80	86.67	80.14	0.966
Metastases	12/89	87.49	90.17	90.67	79.88	0.297
Unknown	4/83	85.04	88.89	81.46	0	NC
Lobe						
Lower	12/92	83.27	86.60	81.82	78.32	0.444
Upper	16/184	84.60	84.97	85.00	85.05	0.749
Middle	0/18	100	0	0	0	0
GTV, cm^3						
<5	14/188	88.43	91.19	81.02	91.14	0.941
5–10	7/54	73.77	66.25	93.33	70.52	0.693
>10	7/46	83.69	87.5	91.67	73.85	0.451
PTV, cm^3						
<15	8/119	92.09	88.64	96.10	95.99	0.439
15–30	6/98	85.3	89.19	64.31	90.96	0.885
>30	14/73	72.5	88.89	82.35	66.96	0.699
PTV/GTV ratio						
<5	17/132	75.99	81.11	76.23	71.87	0.636
5–10	8/107	91.59	90.24	95.92	89.87	0.592
>10	3/49	90.28	100	83.33	87.93	0.496

NC, not calculated; GTV, gross tumor volume; PTV, planning target volume.

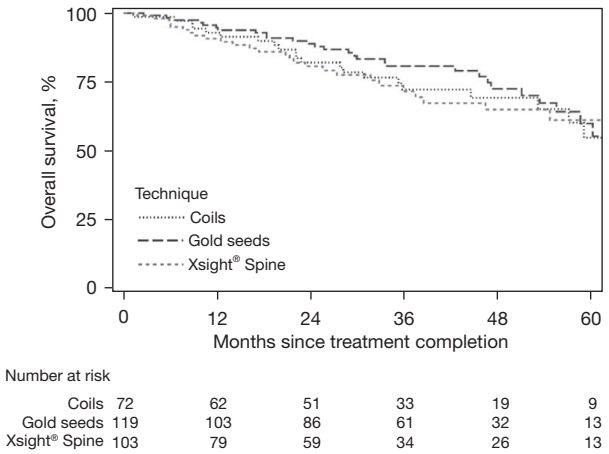

Figure 2 Overall survival according to the tracking technique used.

of 92.22% and 85.35% at two and five years and overall survival rates at two and five years of 84.32% and 59.14%, rates which are consistent with those reported in the literature (13,14,24-26) for CyberKnife® or LINAC-based treatment.

Overall survival, local control, and metastasis-free survival rates did not differ significantly between patients receiving Synchrony® (both type of fiducials) or Xsight® Spine (respectively P=0.586, P=0.685, and P=0.664), which implies that Xsight® Spine is not only noninvasive and safe but also as effective as Synchrony®, in appropriately selected patients, especially in terms of local control. Unlike previously published studies with fewer patients (27,28), the subgroup analysis revealed that local control rates did not differ significantly between techniques within tumors grouped

Table 5 Toxicities

Toxicities	All, N=294	Gold seeds, N=119	Coils, N=72	Xsight® Spine, N=103	P value
Acute toxicities, n (%)					
Pneumothorax					
None	251 (85.37)	76 (63.87)	72 (100.00)	103 (100.00)	<0.001
Grade 1	36 (12.24)	36 (30.25)	0 (0.00)	0 (0.00)	
Grade 2	6 (2.04)	6 (5.04)	0 (0.00)	0 (0.00)	
Grade 3	1 (0.34)	1 (0.84)	0 (0.00)	0 (0.00)	
IAH					
None	285 (96.94)	110 (92.44)	72 (100.00)	103 (100.00)	
Grade 2	9 (3.06)	9 (7.56)	0 (0.00)	0 (0.00)	0.001
Pneumonitis: grade ≥2	4 (1.36)	1 (0.84)	1 (1.39)	2 (1.94)	NC
Cough: grade ≥ 2	2 (0.68)	2 (1.68)	0 (0.00)	0 (0.00)	NC
Dyspnea: grade ≥2	6 (2.04)	1 (0.84)	1 (1.39)	4 (3.88)	NC
Asthenia: grade ≥2	3 (1.02)	0 (0.00)	1 (1.39)	2 (1.94)	NC
Overall: at least one	58 (19.73)	47 (39.50)	3 (4.17)	8 (7.77)	<0.001
Overall except pneumothorax/IAH	15 (5.10)	4 (3.36)	3 (4.17)	8 (7.77)	0.303
Late toxicities % [95% confidence interval]					
Pneumonitis: grade ≥2	0.8% [0.2, 2.9]	0	1.6% [0.1, 7.8]	1.2% [0.1, 5.9]	NC
Cough: grade ≥2	0.5% [0, 2.4]	0	1.6% [0.1, 7.8]	0	NC
Dyspnea: grade ≥2	5.3% [2.9, 8.8]	5.4% [2.0, 11.5]	6.7% [2.1, 15.0)	3.7% [1.0, 9.6]	0.839
Asthenia: grade ≥2	0.4% [0, 2.2]	1.0% [0.1, 5.0]	0	0	NC
Overall: grade ≥2	6.1% [3.5, 9.8]	4.9% [1.5, 11.2]	6.7% [2.1, 15.0]	4.9% [1.5, 11.2]	0.976

IAH, intra-alveolar hemorrhage; NC, not calculated.

by location, GTV, PTV, or PTV/GTV ratio (*Table 4*). This highlights the fact that, even when larger tumors and tumors situated in the lower lobes or with larger PTV seemed to have lower local control rates, the techniques evaluated in this study tended to be equally effective in each of those situations, and so the choice of technique should not depend on these tumor characteristics. However, Xsight® Spine had a nonsignificant tendency to be less effective than the other techniques when the GTV was greater than 10 cm^3 and/or the PTV was greater than 30 cm^3, with respective local control rates of 73.85% and 66.96%. This highlights the need for caution regarding PTV margins and the use of high-performing 4D-CT in these scenarios.

We reported only two acute grade 3 toxicities: one pneumothorax after gold seed implantation and one radiation-induced pneumonitis. One late grade 3 radiation-induced pneumonitis was reported; both cases of pneumonitis resolved after medical treatment. No grade 4 or 5 toxicities were reported. Because of the retrospective nature of our study, we chose to only report grade ≥2 toxicities, which are much more significant for patients than grade 1 and more likely to be reported in EPFs. Surprisingly, symptomatic rib fractures and chest pain were not reported in any patients' files despite having probably occurred in some cases, but none were reported by the patients nor the physician. Acute toxicities differed significantly between groups in terms of pneumothorax and IAH. This directly relates to the transthoracic gold seed implantation only used in the gold seed group; pneumothorax occurred in 36.17% of patients in this group, which is consistent with data from previously published studies (29,30), although only 5.88% of patients in this group required surgery or insertion of a chest tube for a grade 2 or 3 pneumothorax. This highlights the fact that this procedure is not harmless and should be avoided if clinically possible or replaced by navigational bronchoscopy when available, since this procedure seems clinically safer and can achieve biopsy in the same procedure (20). Overall grade ≥2 acute (excluding pneumothorax and IAH) and late toxicity rates did not differ significantly between groups. We tried to conduct a subgroup analysis to account for an effect of GTV size, PTV size, and PTV/GTV ratio on acute and late significant pulmonary toxicities but, due to the limited number of grade ≥2 toxicities, the analysis lacked statistical power and was not performed.

In our population, there were significant differences between the characteristics of the tumors of patients in the gold seed, coil and Xsight® Spine groups in terms of tumor type (metastasis, primary, or unknown; P=0.003), location of primary cancer (P=0.040), and location (P=0.001). This could be explained by the fact that since the pulmonary diameter in the upper lobes is smaller, the treated lesions are more likely to be close to the spine and patients in this setup accessible for spine tracking, most vulnerable patients with non-histologically confirmed tumors were ineligible for lung biopsy and thus ineligible for gold seed implantation, meaning they received noninvasive radiotherapy treatment with Synchrony® using coils or Xsight® Spine. Population groups also differed significantly in PTV size and PTV/GTV ratio. The median PTV volume was 19 cm^3 (IQR, 11.2–31 cm^3) and the median PTV/GTV ratio was 5.5 (IQR, 3.8–8.6); both were significantly different between groups (respectively P<0.001 and P=0.002), which is explained by the fact that patients treated with Xsight® Spine received a 4D-CT scan and ITV-based treatment, resulting in a higher volume of treated lung.

Dosimetric data were significantly different between treatment groups in terms of dose and fractionation regimens (P=0.016), respect to dose constraint thresholds, in particular V10Gy <17% and V5Gy <30% (respectively P=0.002 and P=0.004). Indeed, the Xsight® Spine treatment planning used often more fractionated regimens: 33% of patients in this group received 50 Gy in four fractions versus 19% and 15% of patients in the gold seed and coil groups, respectively, however every patient received regimens with a biologically equivalent dose superior to 100 Gy as clinically recommended (31). Dose thresholds were more frequently exceeded with this technique than with other techniques, particularly for the V10 and V5 values detailed above, where there were significant differences between treatment groups (P≤0.002 and P≤0.004 respectively). This is certainly related to the use of an ITV with Xsight® Spine and therefore a larger PTV for the same GTV size. Although Xsight® Spine used more fractionated regimens, there was no difference between groups in terms of median overall treatment time (P=0.309).

Marker less irradiation is certainly a good noninvasive treatment, but it cannot be performed in all cases. Intravascular marker placement is highly safe and incases where Xsight® Spine cannot be used, markers should be placed intravascularly (32).

To our knowledge, our cohort represents the largest sample size reported to date, and despite the retrospective nature of this study, we were able to suggest that fiducial-less CyberKnife® stereotactic radiation therapy resulted in

satisfactory local control rates, with no significant difference in toxicity between techniques and no significant difference in local control and overall survival rates according to tumor location, GTV, PTV, or PTV/GTV ratio. This study is an actualization of our previous publication (28), reporting survival results and a longer follow-up. We sought to investigate another fiducial-less treatment modality, the Xsight® Lung treatment method. Unfortunately, our center has only used this technique widely since 2018, and not enough patients have been treated with it to perform an adequate analysis. Further research using large sample sizes are needed to investigate this modality.

The main limits of our study are that among others, it's retrospective nature, the lack of clear data about biologically equivalent dose (BED) and dose fractionation, which are correlated with local control in many published studies, and the presence of significant differences between the groups in terms of tumors characteristics could results in difference between groups in terms of local control even if BED was always superior to 100 Gy (33,34).

Conclusions

This study suggests that fiducial-less SBRT using Xsight® Spine offers local control and overall survival rates comparable with those obtained with Synchrony®. Fiducial implantation could therefore be safely avoided, which also offers cost-effectiveness advantages. Noninvasive techniques seems safe to be prioritized whenever possible without, regardless of tumor size or location.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1245/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1245/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by regional ethics committee of Lorraine Cancer Institute (registration No. MR0004) and individual consent for this retrospective analysis was waived.

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