The evolving role of stereotactic ablative radiotherapy in operable early stage non-small cell lung cancer

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N.E. Verstegen
F.J. Lagerwaard
C.J.A. Haasbeek
B.J. Slotman
S. Senan

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Outcomes of stereotactic ablative radiotherapy following a clinical diagnosis of stage I NSCLC: Comparison with a contemporaneous cohort with pathologically proven disease

Abstract

Introduction

As a finding of benign disease is uncommon in Dutch patients undergoing surgery after a clinical diagnosis of stage I NSCLC, patients are also accepted for stereotactic ablative radiotherapy (SABR) without pathology. We studied outcomes in patients who underwent SABR after either a pathological (n = 209) or clinical diagnosis (N = 382).

Materials and methods

Five hundred and ninety-one patients with a single pulmonary lesion underwent SABR after either a pathological- or a clinical diagnosis of stage I NSCLC based on a 18FDG-PET positive lesion with CT features of malignancy. SABR was delivered to a total dose of 60 Gy in 3, 5 or 8 fractions, and outcomes were compared between groups with and without pathological diagnosis.

Results

Patients with pathology had significantly larger tumor diameters ($p < .001$) and higher predicted FEV1% values ($p = .025$). No significant differences were observed between both groups in overall survival ($p = .99$) or local control ($p = .98$). Regional and distant recurrence rates were also similar.

Conclusions

In a population with a low incidence of benign ^{18}FDG-PET positive lung nodules, clinical SABR outcomes were similar in large groups of patients with or without pathology. The survival benefits reported after the introduction of SABR are unlikely to be biased by inclusion of benign lesions.

Introduction

Patients with untreated stage I NSCLC have a poor survival with median survival duration of 10 months, a 1-year survival of 39%, and a 5-year survival of only 2%[1]. At present, surgery is widely considered to be the standard of care in fit patients with an early-stage stage I non-small cell lung cancer (NSCLC), with radiotherapy reserved for patients who are unfit or who decline surgery[2]. In recent years, stereotactic ablative radiotherapy (SABR) has rapidly replaced conventional radiotherapy for this indication in many countries[3]. In a population-based study, the introduction of SABR has been shown to increase the utilization of radiotherapy, particularly in elderly unfit patients, up to 40% of whom were previously untreated[4].

Obtaining a pre-treatment pathological diagnosis in patients presenting with peripheral lung nodules suspicious for lung cancer can be challenging as these lesions are often beyond the reach of conventional bronchoscopy. Consequently, a significant proportion of patients who undergo surgery do not have pre-treatment pathology, despite the known morbidity and mortality accompanying a surgical resection[5–7]. For example, a large Japanese study of 1755 operated patients reported that 27% had no pre-operative diagnosis[7]. Another surgical study reported a lack of pre-operative histological diagnosis in 46% of patients, increasing from 30% prior to 1998 to 55% after 19996.

Although the incidence of complications of a diagnostic transthoracic biopsy, such as pneumothorax and hemoptysis, may be acceptable in fit patients, these are increased in the typical SABR patient populations such as the elderly with severe COPD and other co-morbidities[8,9]. The likelihood of lung malignancy in this setting can be calculated using a combination of patient characteristics and radiological and ^{18}FDG-PET findings[10,11].

In contrast to reports from the United States and Japan[12,13], a higher proportion of patients treated in European reports of SABR do not have a pathological diagnosis[14,15]. Applying this approach to SABR appears justified in a country such as The Netherlands where the diagnosis of benign disease is typically made in only 1–4% of patients undergoing surgery for an ^{18}FDG-PET positive lesion[16–18]. Nevertheless, applying SABR without a prior pathological diagnosis has evoked skepticism and raised questions as to whether local control rates could have been artificially upgraded by the inclusion of benign lesions19. In accordance to Dutch practice guidelines, we accept patients with a high-risk profile for developing lung cancer, either following a pathological diagnosis, or if a clinical diagnosis of stage I NSCLC has been based upon a new or growing ^{18}FDG-PET positive lesion that is

consistent with a primary lung tumor. In this report, we studied the outcomes of SABR for a clinical stage I NSCLC in patient cohorts with a pathological or a clinical diagnosis.

Materials and Methods

A total of 591 patients underwent SABR for a single stage I lung tumor between April 2003 and December 2010 at our center. Patients presenting with a synchronous diagnosis of a second malignancy were excluded from this analysis. Patient-, tumor- and SABR details are prospectively collected in an institutional database, which is constantly updated with follow-up information. All patients underwent pre-treatment tumor staging including CT scans of the chest and abdomen and 18FDG-PET scans. In our prospective database, two patient groups were defined; 209 patients (36% of total) in whom a pathological verification of malignancy was obtained prior to SABR and 382 patients (66%) without a pathological diagnosis (clinical diagnosis). The latter group of patients were accepted for SABR if, in accordance to Dutch practice guidelines, they had all been evaluated by a multidisciplinary tumor board and had findings very suggestive of malignancy.

For the purpose of the present retrospective analysis, the probability of malignancy was calculated for each patient based on a combination of clinical, radiological and FDG-PET findings, as previously described (Table 1). The latter approach has been validated for the Dutch lung cancer population[10,11].

SABR was delivered in an outpatient setting using a risk-adapted fractionation scheme depending on tumor size and location as previously described[14], delivering 60 Gy in 3, 5 or 8 fractions within an overall treatment time of 2 weeks. Individualized target volumes that encompassed all motion on 4-dimensional CT-scans were used for treatment planning. No active motion management (including respiratory gating) was used in these patients. All fractionation schemes used were prescribed to the PTV encompassing 80% isodose and had a biologically effective dose of >100 Gy_{10}. Treatment plans were optimized to limit high dose regions to adjacent organs at risk, such as the chest wall, hilus, mediastinum or heart.

Patients routinely underwent follow-up at 3 months, 6 months, 1 year and annually thereafter. Follow-up CT scans were performed at each visit, but ^{18}FDG-PET scans were repeated only in the event of suspected disease relapse in patients who were fit enough to receive further therapy. In patients unable or unwilling to attend follow-up at our center, the referring lung physician or general practitioner was contacted. In addition, the Dutch

civil death records were used to ensure complete survival data on patients lost to follow-up.

Baseline patient characteristics of both SABR cohorts were compared using the Student t-test and Chi-square test. Treatment outcomes were evaluated using Kaplan–Meier analysis of overall survival, local-, regional- and distant control. Multivariate analysis was performed with Cox regression analysis to investigate the prognostic value of age, gender, tumor stage, fractionation scheme, GOLD COPD classification, WHO performance score, Charlson co-morbidity score, tumor location, history of prior malignancy and history of prior lung cancer. All statistical tests were performed in SPSS version 15.0.

***Table 1**: Probability of malignancy by Swensen et al.[10] and Herder et al.[11]*

Swensen et al.:
Probability of malignancy = 1/(1 + e-x)
In which e is the base of natural logarithms and x is the sum of all coefficients;

Factor	**Coefficient**
Constant	-6.8272
Age	years x 0.0391
Diameter	mm x 0.1274
Smoking	
- Current or former smoker	0.7917
- Never smoked	0
Extrathoracic cancer > 5years ago	
- Yes	1.3388
- No	0
Spiculated lesion	
- Yes	1.0407
- No	0
Location	
- Upper lobe	0.7838
- Other lobe	0

Herder et al.:
Probability of malignancy = 1/(1 + e-x)
In which e is the base of natural logarithms and x is the sum of all coefficients;

Coefficient	**Factor**
Constant	-4.739
Probability by Swensen	probability x 3.691
PET uptake (SUV)	
- Faint uptake	2.322
- Moderate uptake	4.617
- Intense uptake	4.771

Results

A total of 591 patients underwent SABR for stage I NSCLC; 60% male and 40% female, with a median age of 74 years. Ninety-five percent of patients were current or former smokers and 79% of patients had a history of chronic obstructive pulmonary disease (COPD) with a mean FEV1 value of 64% of their predicted values. A history of prior malignancy was present in 34% of all patients, of which approximately 50% had previously been treated for lung cancer. Relevant baseline characteristics of both groups are summarized in Table 2. Both patient cohorts were well balanced with respect to age, gender, Charlson co-

morbidity score, smoking history and performance score.

In patients with a pathological diagnosis of lung cancer, tissue was obtained by transthoracic biopsy in 138 patients (66%) and via bronchoscopy in the remaining 71 patients. Histologies were squamous cell carcinoma (35%), adenocarcinoma (32%) and NSCLC, not further specified, in 33%. Patients with a clinical diagnosis had a median age 74 years; 95% had a history of smoking and 95% had typical spiculated lesions on diagnostic chest CT scans. Patients with a clinical diagnosis had a significantly smaller mean tumor diameter than patients with a pathological diagnosis (28.4 mm versus 34.2 mm, $p < .001$). Furthermore, patients with only a clinical diagnosis had poorer baseline pulmonary function, with a mean predicted FEV1 of 62.1% versus 66.9% ($p = .025$).

Median follow-up, calculated according to the inverse Kaplan–Meier method, for patients with a pathological diagnosis was 32.8 and 29.5 months for patients with a clinical diagnosis20.

The abovementioned approach for calculating the probability of malignancy resulted in a mean probability of malignancy of 92.5% (95% CI 91.8–93.3%) in patients without a pathological diagnosis and 93.2% of these patients had a calculated probability of malignancy that exceeded ≥ 80 (Fig. 1)[11]. In the subgroup of patients with a pathological diagnosis, the corresponding calculated mean probability of malignancy was 94.8% (95% CI 94.2–95.4%).

An outcome comparison between both patient cohorts is shown in Fig. 2 and Table 3. The median OS of patients with and without pathology did not differ significantly and was 39.2 and 40.2 months, respectively ($p = .999$). Corresponding OS rates at 3 years follow-up were 53.7% and 55.4%. No difference was observed between both groups with respect to both regional- ($p = .947$) and distant control ($p = .980$). Because significant differences in T-stage existed between both groups, a separate analysis was performed within the T1 and T2 tumors. No differences in OS could be found between the clinical and pathological diagnosis group for both T1 ($p = .86$) and T2 tumors ($p = .42$). In addition, a multivariate analysis for OS using age, gender, tumor stage, pulmonary function and pathological or clinical diagnosis showed that none of these factors, including pathology ($p = .66$), were significantly correlated with OS.

Tabel 2: *Patient characteristics*

	Clinical diagnosis No (%)	**Pathological diagnosis No (%)**	**P-value**
Gender - Male - Female	 233 (61%) 149 (39%)	 122 (58%) 87 (42%)	N.S.
Age (in years, median)	74 (range 47 – 91)	74 (range 47 – 90)	N.S.
Stage - T1N0M0 - T2N0M0	 232 (61%) 150 (39%)	 83(40%) 126(60%)	P <.001
Diameter (mm, mean)	28.4 mm (range 10-89)	34.2 mm (range 11-80)	P<.001
Fractionation scheme: - 3x20Gy (3x18Gy) - 5x12Gy (5x11Gy) - 8x7.5Gy	 157(41%) 150(39%) 75(20%)	 49(23%) 111(53%) 49(23%)	N.S
Smoking (current of former) - Yes - No - Unknown	 364 (95%) 9 (2%) 9 (2%)	 200 (96%) 6 (3%) 3 (1%)	N.S.
GOLD - 0 - I - II - III - IV	 79 (21%) 42 (11%) 118 (31%) 108 (28%) 35 (9%)	 48 (23%) 25 (12%) 79 (38%) 43 (21%) 14 (7%)	N.S.
FEV1% predicted (mean)	62% (range 16 – 130%)	67% (range 18 – 129%)	P = .025
Charlson co-morbidity (median)	2 (range 0-11)	2 (range 0-9)	N.S.
WHO score - 0 - 1 - 2 - 3	 42 (11%) 185 (48%) 32 (35%) 23 (6%)	 19 (9%) 110 (53%) 72 (34%) 8 (4%)	N.S.
Inoperable - Yes - No	 265 (69%) 117 (31%)	 150 (72%) 59 (28%)	N.S.
Histology - Adenocarcinoma - Squamous cel - NSCLC not further specified		 67 (32%) 73 (35%) 69 (33%)	

Figure 1: *Distribution of the calculated likelihood of malignancy for patients with either a pathological or clinical diagnosis, based on clinical, radiological and FDG-PET findings*

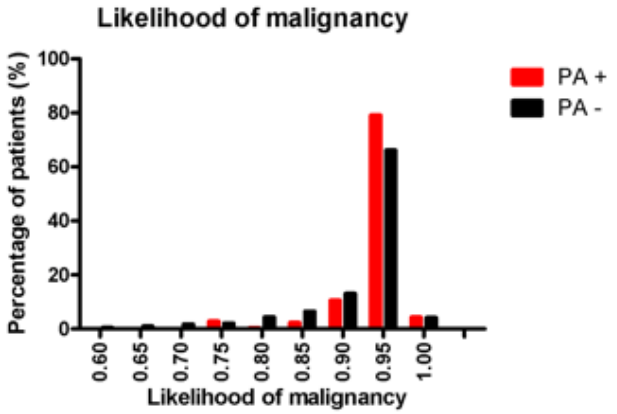

Figure 2: *Comparison of overall survival (left upper), local control (right upper), regional control (left lower) and distant control (right lower) for patients with a pathological versus patients with a clinical diagnosis*

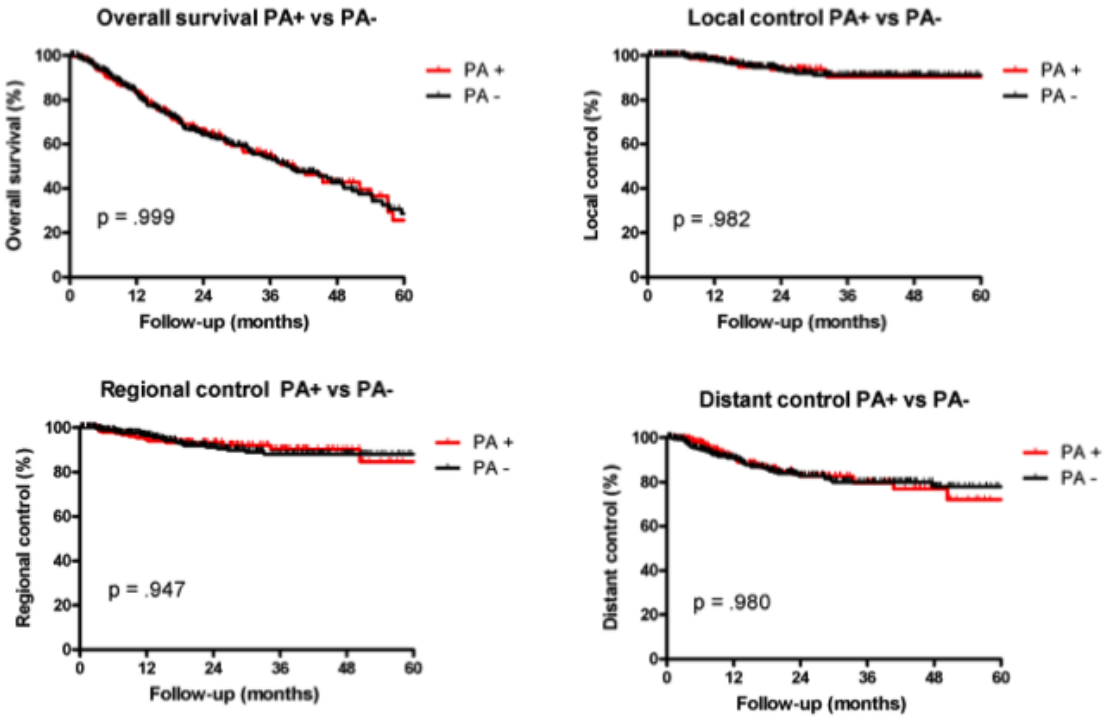

Table 3: *Comparison of outcome parameters at 3 years follow-up*

3-year endpoints	Clinical diagnosis	Pathological diagnosis	P-value
Overall survivall	53.7%	55.4%	p = .999
Local control	91.2%	90.4%	p = .982
Regional control	88.1%	90.3%	p = .947
Distant control	73.0%	79.6%	p = .980

The local control rate at 3 years following SABR was comparable in both patient cohorts (90.4% vs. 91.2%; p = .982), with local failures observed in 10 and 18 patients in patients with a pathological or clinical diagnosis, respectively. A sub-analysis showed no differences in LC between both groups within the T1 (p = .89) or T2 tumors (p = .62).

As benign granulomas were considered unlikely to shrink after SABR, we also assessed the percentage of patients with stable disease on CT scans according to the RECIST criteria at 6 and 12 months after SABR[21]. In patients with a pathological diagnosis, follow up scans at 6 and 12 months were available and evaluable in 81.6% and 67.6% of living patients, respectively. Stable disease was seen in 3.9% (6/154) and 1.7% (2/118) of these scans at 6 and 12 months. In patients with a clinical diagnosis, the corresponding rates of stable disease was 3.5% (9/257) at 6 months and 3.7% at 12 months (8/216).

Severe (CTCAE grade ≥ 3) late toxicity was uncommon in both patient cohorts. A total of 18 patients (3%) developed grade ≥ 3 radiation pneumonitis, 10 patients showed rib fractures on follow-up scans (2%) and three patients experienced grade ≥ 3 chest wall pain (1%). No significant difference in side-effects could be demonstrated between both patient groups

Discussion

The main findings of the present study were that local control rates exceed 90% at 3 years follow-up in both patients with and without a pathological diagnosis. Comparable local control and response rates in such patients were also reported in two previous studies, both of which included far fewer patients (n = 86 and 57, respectively) than the present series[22,23]. Equally important is the low incidence of high-grade toxicity reported when SABR is applied in elderly patients with significant co-morbidities[14,24,25].

A failure to obtain a pathological diagnosis before treatment is not limited to the SABR literature. A large recent Japanese surgical study reported a lack of pre-operative

histological diagnosis in 46% of patients, a percentage which increased from 30% prior to 1998 to 55% after 1996. The 516 patients without pre-operative pathology in this Japanese study included those with very small lesions in which malignancy was considered likely based on the clinical images, as well as those cases with inconclusive findings after biopsy. In this second subgroup of patients, histological examination after surgery demonstrated benign lesions in 13%. However, it should be pointed out that Sawada et al. did not routinely perform ^{18}FDG-PET scans, and that a large proportion of their patients had been referred via screening studies.

The differences between our SABR population and participants in CT screening studies for lung cancer must be appreciated. Most screening studies only accrue heavy smokers aged 50 years or older who are fit enough to undergo surgery, while the median age in our patients without histology was 74 years, with 69% considered to be medically inoperable. Furthermore, all of our patients with a clinical diagnosis had lesions measuring ≥ 10 mm, with the mean lesion size being 28.4 mm. In contrast, the mean lesion diameter reported in most screening studies is 10–18 mm with a substantial incidence of lesions <10 mm26–28.

The guidelines of the American College of Chest Physicians on the management of solitary pulmonary nodules recommend that a calculated likelihood of malignancy which exceeds 60% warrants treatment without further diagnostic procedures[2]. Several validated calculation models for assessing this probability have been reported and the findings of ^{18}FDG-PET imaging have been incorporated into the model first reported by Swensen et al. This calculation model was used in this current study[11]. The probability of malignancy in our patients with only a clinical diagnosis was 92.5%, which was similar to that in contemporaneous group with a pathological diagnosis.

The use of such risk calculation models may be less appropriate for patients living in regions where infections, such as histoplasmosis, can give a false-positive PET uptake, thus reducing the specificity of ^{18}FDG-PET scans. A recent American retrospective study of 96 patients, who underwent surgery for an ^{18}FDG-PET positive lesion, indicated that failure to account for both CT- and PET characteristics indicative of malignancy could result in more patients with benign lesions undergoing surgery[29]. Besides the tumor diameter, the majority of patients in the current report with a clinical diagnosis had lesions which showed growth on repeated CT scans. Although we recognize that the latter does not exclude the possibility of a benign lesion, it does decrease the probability of accepting granulomas for SABR. Similarly, as granulomas are unlikely to decrease substantially in

size following SABR, we studied the number of patients with stable disease on follow-up CT scans according to RECIST criteria[21]. In the patients with a clinical diagnosis, the rates of patients with stable lesion size were only 3.5% and 3.7% at 6 months and 1 year, respectively. This percentage of patients with stable disease after SABR corresponds well with both the calculated likelihood of malignancy in this patient cohort, as well with the reported rates of benign lesions reported in Western European surgical studies. Our patients were referred via multidisciplinary boards which also identify patients for surgical resection. The low reported rates of benign lesions in Western European surgical studies illustrate the appropriateness of the patient selection procedure by these boards[16–18,30].

Some limitations of our study have to be mentioned. A substantial proportion of all patients (34%) had a history of prior malignancy and approximately 50% of these patients had previously been treated for lung cancer. Although 96% of our patients had spiculated lesions and the interval between the prior malignancy and SABR was longer than 2 years in 75% of these patients, the possibility remains that some patients were treated for a single pulmonary metastasis instead of a primary lung tumor[31]. However, as all of our patients underwent ^{18}FDG-PET staging, these patients must have had 'oligometastatic' disease, which is an accepted indication for SABR[32–34]. Although it remains possible that <5% of treated patients with a clinical diagnosis actually had benign disease, the low incidence of grade ≥ 3 toxicity following SABR has to be weighed against the complication rate of invasive diagnostic procedures in this high-risk patient group.

In conclusion, in a Dutch population with a low incidence of benign ^{18}FDG-PET positive lung nodules, the clinical outcomes following SABR were similar in patients either with or without a pathology-proven diagnosis of stage I lung cancer. Although a pathological diagnosis should be obtained whenever possible, this remains challenging in frail patients who present with small peripheral lung lesion. Our findings indicate that early treatment of such patients is justified after review within a multi-disciplinary tumor board.

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