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**Review Article**

# Prognostic Probability of FDG-PET before Stereotactic Ablative Radiotherapy for Primary Lung Cancer -Review of the Literature

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**Abstract**

Stereotactic Ablative Radiotherapy (SABR) is developing and becoming one of the few curative treatment methods alternative to resection for early-stage lung cancer in inoperable patients. FDG-PET now has many approved indications and is included in guidelines for tumor staging and response assessment. FDG-PET is also used for radiotherapy in lung cancer in many ways (e.g., target delineation, prediction prognosis); however, there are some limitations, especially motion blur and partial volume effect. Thus prognostic ability of SUVmax is controversial in early-stage lung cancer. We reviewed the utility and limitation of FDG-PET in SABR for early-stage lung cancer.

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## ABBREVIATIONS

SABR: Stereotactic Ablative Radiotherapy; PET: Positron Emission Tomography; FDG: $^{18}$F-fluoro-2-Deoxy-D-Glucose; SEER: Surveillance, Epidemiology and End Results; RTOG: Radiation Therapy Oncology Group; BED: Biologically Equivalent Dose; RTRT: Real-time Tumor-tracking radiotherapy; TOF: Time-of-Flight; SUV: Standardized Uptake Value; T/N: Tumor-to-Normal ratio; NSCLC: Non-Small Cell Lung Cancer; SUVmax: Maximum Standardized Uptake Value; RC: Recovery Coefficient

## INTRODUCTION

Stereotactic Ablative Radiotherapy (SABR) in the trunk

was reported by Blomgren et al. [1] of the Karolinska Institute in 1995. SABR is becoming one of the few curative treatment methods as alternatives to resection for early-stage lung cancer in inoperable patients.

Positron Emission Tomography (PET) is able to image multiple functional parameters depending on the radiotracer used. $^{18}$F-fluoro-2-deoxy-D-Glucose (FDG) is the most commonly used radiotracer for diagnosis of malignancy. FDG-PET now has many approved indications and is included in guidelines for tumor staging and response assessment. FDG-PET is also used for radiotherapy in lung cancer in many ways (e.g., target delineation and prediction prognosis).

We reviewed the utility and limitations of FDG-PET in SABR for early-stage lung cancer.

## SABR for early-stage lung cancer

SABR is an irradiation method to deliver high dose of radiation to a spot with a multi-dirrection and/or multi-arc beam arrengement by recently developed tecnology for radiotherapy. It was reported that results of SABR for early-stage lung cancer, including not only local control but also oveall survival, were superior to those of conventional radiotheapy [2-4]. Recently, many institutions have reported treatment results. The treatment methods and results of treatment in representative institutions are summurized in Table 1 [5-9].

Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare cohort spanning 2001-2007, Shirvani et al. compared survival outcomes associated with 5 strategies used in contemporary practice: lobectomy, sublobar resection, conventional radiation therapy, SABR, and observation. The results with propensity-score matching showed that SABR was comparable to surgery in select populations and the conventional radiation was associated with poor outcomes [4]. Verstegen et al. showed superior local control rate after SABR compared with VATS in propensity score-matched analysis [10]. SABR is recognized as one of the few curative treatment methods as alternatives to resection for early-stage lung cancer in inoperable patients. Recently, Machtay et al. in a review of 1356 Radiation Therapy Oncology Group (RTOG) lung cancer patients found an estimated 4% decrease in the risk of death with every 1 Gy increase in Biologically Equivalent Dose (BED) with increasing risk of radiation disorder [11].

In SABR in the trunk, in contrast to the brain, management against respiratory motion during irradiation is necessary, especially to reduce radiation disorder. The applicability of respiratory gating in radiotherapy was first studied in Japan in the late 1980s [12]. Such technology is developing and there are some specified treatment systems for SABR (e.g., Cyberknife). Most of such radiotherapy systems using tumor position prediction are based on surrogate breathing signals with a reflective marker on the abdominal wall. However, tumor position prediction is not so simple because of regular breathing, frequency changes, baseline shifts, amplitude changes, cardiac motion and combination patterns. Shirato et al. developed a method called Real-Time Tumor-Tracking Radiotherapy (RTRT) that consists of (1) real-time monitoring of tumor position using tracking technology in computer science and (2) instantaneous irradiation technology [13]. The linear accelerator with RTRT is gated to irradiate the tumor only when the fiducial marker is within ± 2 mm from its planned coordinates relative to the isocenter, and the system recognizes the 3-D coordinates of the fiducial marker in or around the tumor 30 times/s using two fluoroscopic X-ray systems. Recently, SIMADZU Corp. developed a new-generation RTRT system (Product name: SyncTraX) jointly with Shirato et al. This system has many improvements compared to conventional RTRT (including tracking multiple fiducial markers and image processing for fluoroscopy with a wide coverage). That system might be the most reliable system among existing radiotherapy systems against respiratory motion.

## Features of a PET scanner

Each annihilation produces two 511 keV photons traveling in opposite directions and these photons can be detected by detectors surrounding the subject. Tissue attenuation correction is performed by recording a short transmission scan (Transmission scan) using γ-rays from three radioactive (Germanium-68/Gallium-68) rotating rod sources or CT. Recently, several technologies have been introduced to a PET camera for improving image quality. For example, TOF (time-of-flight) technology uses the actual time difference between the detection of coincident events to more accurately identify the origin of the annihilation. Better identification leads to a quantifiable improvement in image quality. Furthermore, a without septa ("3D mode") transmission scan has a much stronger variation in sensitivity, which peaks in the center of the axial FOV. The resolution of the latest PET camera (full width at half maximum) is 4-5 mm. Several new technologies for a PET scanner have been reported (e.g., CdTe semiconductor detectors, depth-of-interaction system) [14,15]. By using these new technologies, it should be possible to obtain high-quality PET images with low scatter noise and high spatial resolution.

In regard to quantity, the Standardized Uptake Value (SUV) and Tumor-to-Normal ratio (T/N) are commonly used

**Table 1:** Summary of treatment methods and results of SABR for early-lung cancer in representative institutions.

| Author [reference No.] | Number of Patients | Total dose (Gy) | Single dose (Gy/fr.) | BED10 (Gy) | Median follow-up period (months) | Local control rate (%) | 3-year overall survival (%) |
|---|---|---|---|---|---|---|---|
| Timmerman [5] | 55 | 60 | 20 | 180 | 34.4 | 98.2 | 55.8 |
| Nagata [6] | 42 | 48 | 12 | 105.6 | 30 | 97.8 | 83 |
| Fakiris [7] | 70 | 60, 66 | 20, 22 | 180 - 211.2 | 50.2 | 94.3 | 42.7 |
| Onishi [8] | 257 | 18 - 75 | 4.4 - 35 | 57.6 - 180 | 38 | 88.7 | 56.8 |
| Shirata [9] | 80 | 48 - 60 | 4 -12 | 84 - 105.6 | 30.4 | 92.5 | 89.9 |

parameters for semi-quantitative evaluation of tracer uptake in tumors. However, quantification in early-stage lung cancer indicated for SABR is underestimated because of insufficient count recovery. That is called "partial volume effect". Count recovery means ratio activity observed in the Volume-of-Interest (VOI) to true activity in the VOI. A diameter of at least 3-4 cm is needed for full recovery in PET. An artifact caused by tumor motion during an emission scan (motion blur) has a great effect on quantitative performance [16]. PET imaging of the lung and abdomen region is generally affected by patient respiratory motion, which can lead to underestimation of the maximum standardized uptake value (SUVmax) of a region of interest, overestimation of tumor volume, and mismatched PET and CT images that yield attenuation correction errors, registration errors and tumor mislocalization [17-19]. Some PET systems with measures for motion blur (e.g., 4D-PET/CT) have recently been developed.

## Utility of FDG-PET for primary lung cancer

In recent years, FDG-PET/CT has been repeatedly reported to improve overall staging of non-small cell lung cancer (NSCLC) patients by allowing the acquisition of co-registered, spatially matched functional and morphological data [20-22]. There is no longer any doubt about the usefulness of FDG-PET/CT in lung cancer. There have in fact been many patients in whom irradiation fields were changed on the basis of PET information. Even in early-stage lung cancer, Li et al. reported that the sensitivity, specificity, accuracy, Positive Predictive Value and negative predictive value of FDG-PET/CT for lymph node metastases were 44%, 83%, 78%, 29% and 91%, respectively. They concluded that FDG-PET/CT may help to accurately stage N0 patients and thus identify patients who are candidates for SABR [23]. As well as staging, FDG-PET/CT is also useful for predicting prognosis and evaluating the treatment effect [24].

Furthermore, many investigators have reported various methods for incorporating PET into the radiation treatment plan. In recent studies, some threshold values (percentage of SUVmax or absolute SUV) were used to define the tumor boundary [25]. At least, FDG-PET/CT significantly reduced observer variation in lung cancer delineation with respect to CT only [26,27].

However, many factors affect SUV measurements and therefore tumor contours. In early-stage lung cancer, Biehl et al. and Caldwell et al. showed that the stereotypical threshold is inappropriate because of tumor size and/or respiratory motion [28,29].

## Prognostic probability of FDG-PET in patients with early primary lung cancer treated with sterotacitic radiotherapy

Some prognostic factors (e.g., T stage, $BED_{10}$ and minimum dose of PTV) were SABR for early-stage lung cancer have recently been reported. The prognostic value of SUVmax has also discussed. Some investigators reported that SUVmax was an independent predictor of local control after SABR in stage I NSCLC, while other investigators reported that it was not an independent predictor. Hamamoto et al. and Takeda et al. reported that local control rates for lower SUVmax and higher SUVmax were significantly different [30,31]. On the other hand, Burdick et al., Abelson et al. and Satoh et al. reported that SUVmax did not affect local recurrence after SABR [32-34].

However, as mentioned above, there are two large artifacts causing underestimation of FDG accumulation in small tumors indicated for SABR. The correlation between local control and SUVmax must be examined after correction those two artifacts. Bundschuh et al. described a method that improves the quantification of moving lesions by local motion correction using list-mode data without increasing acquisition time or reducing signal-to-noise ratio of the images [35]. Stiles et al. reported a correlation between prognosis after resection and ratio of SUVmax to tumor size [36]. Results in 530 patients showed that patients with higher SUVmax/size ratio had significantly poorer disease-free survival. Ohtaka et al. reported that SUVmax was able to predict outcome in patients with early-stage NSCLC treated by resection [37]. However, in those two studies [36,37], in which there was no correction of motion blur, a correlation between SUVmax/tumor size ratio and local control was not shown and the patients were not treated by SABR. To the best of our knowledge, there has been no paper in which prognosis after SABR with correction both of those artifact is described. We previously reported the results of a phantom experiment and attempted to estimate the Recovery Coefficient (RC) for both partial volume effect and respiratory motion blur and to establish formulas (below) for simple correction of these factors [38].

$$RC(x,y)=\frac{a}{1+b\times\exp(-cx)}\times\exp\left(\frac{-y}{f}\right)\text{(Sphere diameter <13 mm)}$$

$$RC(x,y)=\frac{a}{1+b\times\exp(-cx)}\times\exp\left(\frac{-y}{dx+e}\right)\text{(Spherediameter <13 mm)},$$

where x is sphere diameter, y is motion amplitude, and a, b, c, d, e and f are constants.

We are preparing a paper for publication in which the possible prognostic value of SUVmax is reassessed after correction of both partial volume effect and respiratory motion blur using the above formulas in patients with stage I NSCLC treated by SABR in our institution. A prospective study using 4D-PET is also need, although partial volume effect must also be considered.

## Utility of FDG-PET after SABR

CT changes after SABR can develop as mass-like patterns that mimic the appearance of recurrent disease [39,40]. Therefore, there were many cases in which it was impossible to distinguish recurrence/residual from radiation-induced inflammatory change. With FDG-PET, this has been very difficult because FDG accumulates moderately also in inflammatory lesion. Some investigators have reported methods to distinguish recurrence/residual using FDG-PET. A systematic review by Huang et al. provided descriptions of anatomic and metabolic lung changes after SABR [41] suggesting that a) SUVmax associated with recurrence may fail to decline or may increase over time sometimes after an initial fall and b) recurrence after SABR generally correlates with sequential opacity enlargement on follow-up CT imaging and SUVmax of 5 or more, and if a scan is performed 3-6 months after SABR in an attempt to predict

response, then an SUVmax of 5 or more is also associated with a higher risk of recurrence.

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