

# Stereotactic ablative radiotherapy (SABR) in operable early stage non-small cell lung cancer (NSCLC) patients: challenge to claim being undisputed gold standard

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The standard treatment for operable, early stage non-small cell lung cancer (NSCLC) is surgical resection, usually lobectomy, with mediastinal lymph node sampling or dissection. However, significant surgical toxicity had been noted in these patients with 90-day mortality rates exceeding 30-day rates (1). There is also a risk of disease recurrence ranging from 6% to 10% per person-year during the first 4 years after surgery as stated by Lou *et al.* after an analysis of 1,300 patients who underwent surgery (2).

A substantial proportion of early-stage lung cancer patients are not suitable for surgery due to their coexisting serious medical problems, older age, and poor performance status. Conventional radiotherapy is only modestly effective in these patients. Over the past decade, stereotactic body radiation therapy (SBRT), which uses highly conformal multiple noncoplanar beams for the precise delivery of high doses per fraction, has emerged as a promising treatment alternative in the management of these frail patients with early-stage disease with acceptable outcomes noted to be better than conventional radiotherapy. In recent years, the prescription of truly ablative radiation doses has been professed as stereotactic ablative radiotherapy (SABR) (3,4). Several technological advances in patient positioning and immobilization systems, tumor motion assessment and control, target delineation, image guidance for precise targeting, and treatment planning systems facilitated the use of SABR in the treatment of many organ cancers and metastases. The delivery of very high biologically effective doses in a fewer actual treatments is also more convenient for the patients.

There has been an ongoing evolution in SABR to define the toxicity and efficiency limits to be safely delivered. As many medically inoperable patients have limited lung functions, it was relieving to observe that SABR for medically inoperable stage I lung cancer did not cause any major deterioration in pulmonary function tests even in severe chronic obstructive pulmonary disease (5,6). Another step was to define the minimum dose of SABR for local control, and Onishi and colleagues draw the line for better local control and survival rates with a minimum calculated biological effective dose (BED) of 100 Gy in their Japanese multi-institutional study (7). On defining the safety limits, Timmerman *et al.* reported excessive toxicity when treating centrally located tumors near the central airways with 54-60 Gy in 3 fractions, and determined a “SABR no-fly zone” (8). However, risk-adapted SABR schedules were reported to be considered safe in this zone with well tolerability and less toxicity via more than 3 fractions of SABR and more detailed recommendations have been announced to delineate how to fly in a “no fly zone” by SABR (9,10). As the ongoing Radiation Therapy and Oncology Group (RTOG) 0813 phase I trial for centrally located tumors is expected to determine the maximum tolerated dose in 5 fractions based on risk-adapted dosing strategies Advanced Radiation Technology Committee of the International Association for the Study of Lung Cancer recently published the up-to-date boundaries of indications, dose regimens, planning optimization, and normal tissue dose-volume constraints for 4, 5, and 10 fractions including critical structures such

as bronchial tree, esophagus, major vessels, heart, and the brachial plexus/phrenic nerve for prescribing SABR to treat central NSCLC (11).

The landmark study RTOG 0236 determined the role of SABR for medically inoperable patients with moderate treatment-related morbidity. RTOG 0236 trial with 34.4 months of follow-up indicated a 3-year primary tumor control rate of 98%, a locoregional control rate of 87%, 3-year local (tumor plus lobe) control rate of 91%, and a median overall survival (OS) of 48 months in 55 medically inoperable, peripherally located early-stage NSCLC patients (12). The survival contribution of SABR to these surgically untouchable patients whose natural survival history without treatment would be a median of 13 months for a T1N0M0 patient was encouraging (13). Multiple similar retrospective or prospective studies from several cooperative groups around the world reported similar local control and survival rates with several total dose and fractionation schemes (9,14-16). The results of these studies have clearly proven that SABR should be the new standard treatment for patients with early-stage NSCLC who are unable to tolerate surgery.

Despite encouraging results in medically inoperable patients the introduction of SABR to operable early stage patients instead of gold standard surgery has been a challenging issue. On one hand there is an invasive but a proven treatment option, and on the other hand there is a noninvasive, more convenient but an unproven treatment option leading to similar results. The search for whether similar promising outcomes could be observed in medically operable patients started with retrospective analysis of series including potentially operable patients. Onishi *et al.* retrospectively pointed out successful results for medically operable early stage NSCLC patients in their multi-institutional database, while Lagerwaard *et al.* emphasized a more than 5 years median OS for patients with potentially operable disease who underwent primary SABR (17,18). The Japan Clinical Oncology Group (JCOG) documented their phase II trial of SABR (JCOG 0403) for operable peripheral stage IA NSCLC with a 3-year survival rate of 76% and a 3-year locally progression-free survival rate of 69% in patients with a median age of 79 years old (19).

As there was no prospective randomized data on SABR, series and retrospective reviews using matched-pair analysis and propensity score comparisons, and a systematic review in clinical stage I NSCLC treated with surgery or SABR were published after 2012 (20-22). Interestingly these series reported no differences in OS, local or locoregional control

between surgery and SABR, and even superior locoregional control with SABR. A recent survival meta-analysis covering 40 SABR studies (4,850 patients) and 23 surgery studies (7,071 patients) also pointed out no difference in OS and disease free survival after adjustment for age and operability in operable stage I NSCLC (23).

These provocative results have led to the initiation of three randomised trials comparing SABR with lobectomy (STARS, ROSEL) or sublobar resection (ACOSOG Z4099/RTOG 1021) in order to finalize the challenge between surgery and SABR in operable patients. Radiation oncologists and thoracic surgeons have been waiting the results of these randomised trials eagerly in order to call time on the argument about the issue of SABR or surgery for operable stage I patients. However, both due to the limited number of operable patients and the reluctance of patients and doctors for randomisation between two completely different treatments, these trials were terminated early due to poor accrual, and no report was published about these trials until the current paper by Chang *et al.* which reported the combined results of randomized STARS and ROSEL trials comparing SABR with lobectomy for operable stage I patients (24). The authors are to be congratulated for their effort combining the data of these two trials. Fifty-eight patients with clinical T1-T2a (<4 cm), N0M0, operable NSCLC were enrolled and randomly assigned to SABR (31 patients) or lobectomy with mediastinal lymph node dissection or sampling (27 patients). Histological confirmation of NSCLC was required in the STARS trial but was not mandatory in the ROSEL trial which included only Dutch patients. In the STARS protocol CyberKnife system was used to deliver SABR, whereas linac-based SABR from multiple vendors was used in the ROSEL protocol. In the STARS trial 54 Gy in 3 fractions in peripherally located tumors, and 50 Gy in 4 fractions in central lesions were applied. In the ROSEL trial 54 Gy in 3 fractions or 60 Gy in 5 fractions were applied. Median follow-up for all patients was 40.2 months in the SABR group and 35.4 months in the surgery group. Pooled estimated OS at 3 years favored SABR group (95% *vs.* 79%;  $P=0.037$ ). The difference in OS between two groups was significant in STARS alone ( $P=0.0067$ ) but not in ROSEL ( $P=0.78$ ). One patient in the SABR group, and two patients in the surgery group had distant metastasis at 3 years ( $P=0.42$ ). Recurrence-free survival at 3 years also favored SABR group but the difference was not significant (86% *vs.* 80%;  $P=0.54$ ). At 3 years 96% of patients were free from local recurrence in the SABR group compared

with 100% of patients in the surgery group ( $P=0.44$ ). But the statistical power of this study to detect significant differences in terms of local, regional, and distant failure between the two groups was low due the small number of events in a small patient population with a short follow-up duration. Only one death occurred within the SABR group in contrast to six deaths in the surgery group; and the lower survival rate following surgery was suggested to be related with other co-existing conditions worsened by the surgical reduction of lung function. Three patients (10%) in the SABR group developed grade 3 treatment-related toxicity without any grade 4 or 5 toxicity seen. One patient (4%) in the surgical group died of surgical complications and 12 patients (44%) had grade 3-4 treatment-related toxicity.

One of the common criticisms for SABR studies has been lack of tissue diagnosis before treatment. In this current pooled analysis, this issue could be brought up as histological confirmation by biopsy or cytological evaluation was necessary in the STARS trial whereas was not mandatory in the ROSEL protocol. But numerous studies already clearly justified the treatment without a pathologic diagnosis if a tissue diagnosis is not possible to safely obtain and there is enough clinical, and/or metabolic/radiographic evidence to predict progressive tumor (25,26). On the other hand, the tissue diagnosis could be pursued in an operable patient population in future trials which would still be a great contribution for future possible personalized medical treatment based on molecular/genetic prognostic and predictive biomarkers for targeted medications. Then again, the lack of surgical staging (mediastinal sampling, dissection) in SABR patients, aside from clinical staging with CT, PET-CT, and endobronchial ultrasonography, did not cause any deterioration in locoregional control or OS with SABR in this pooled analysis, and a surgical myth on criticizing radiation oncologists is almost over.

The findings of this study are consistent with the findings from the previous studies concluding that two treatment options are at least equal and SABR should also be considered as a treatment option in operable stage I patients. Finally the results of this study are encouraging the clinicians to facilitate a large clinical trial to investigate a fair comparison of SABR versus surgery in early-stage operable NSCLC patients after lost years of discussion to limit SABR in only medically inoperable patients.

One can claim that it is time to have another big step in the treatment evolution of early stage NSCLC which might add SABR as equipose gold standard to the standing alone gold standard surgery. According to the reported data so far,

good oncologic outcome, and low toxicity of SABR will lead to limitation of the use of surgery in the treatment of stage I NSCLC in the future.

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