

Stereotactic ablative radiotherapy for medically inoperable early stage lung cancer: early outcomes

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Objective To evaluate the clinical outcome and safety of stereotactic ablative radiotherapy for medically inoperable stage I non-small-cell lung carcinoma.

Design Retrospective case series.

Setting Pamela Youde Nethersole Eastern Hospital, Hong Kong.

Patients All patients with medically inoperable stage I non-small-cell lung carcinoma receiving stereotactic ablative radiotherapy since its establishment in 2008.

Main outcome measures Disease control rate, overall survival, and treatment toxicities.

Results Sixteen stage I non-small-cell lung carcinoma patients underwent the procedure from June 2008 to November 2011. The median patient age was 82 years and the majority (81%) had moderate-to-severe co-morbidity based on the Adult Comorbidity Evaluation 27 index. With a median follow-up of 22 months, the 2-year primary tumour control rate, disease-free survival and overall survival rates were 91%, 71% and 87%, respectively. No grade 3 (National Cancer Institute Common Terminology Criteria for Adverse Events) or higher treatment-related complications were reported.

Conclusion Stereotactic ablative radiotherapy can achieve a high degree of local control safely in medically inoperable patients with early lung cancer.

New knowledge added by this study

- Stereotactic ablative radiotherapy is a safe and effective novel technique for early stage medically inoperable lung cancer in our locality, and is tolerated even by elderly patients with multiple co-morbidities.

Implications for clinical practice or policy

- Patients with early stage non-small-cell lung cancer but having high surgical risks should be assessed by clinical oncologists to consider offering stereotactic ablative radiotherapy.

Introduction

Conventional radiotherapy (RT) has been regarded as an inferior substitute to surgery in early stage non-small-cell lung cancer because of its lower rates of local control and overall survival (OS) compared to lobectomy with systematic lymph node dissection. Its reported median local failure rate was 40%, and the 3-year OS and cause-specific survival rates were reported to be 34 and 39%, respectively.¹ On the contrary, surgery offered better survival outcomes in stage I disease with 5-year OS rates generally being greater than 50% (52-89%).²⁻⁵ While inferior OS in these case series can be partially explained by selection biases, inferior local control can be attributed to factors like inadequate radiation dose, inaccurate patient setup, suboptimal treatment verification, and failure to precisely account for respiratory motion.

With the advances in technology, new systems like Active Breathing Coordinator (Elekta, Stockholm, Sweden) or Real Time Position Management (Varian Medical Systems, Palo Alto [CA], US) are now available to take account of respiratory motion. Systems like ExacTrac (BrainLAB, Heimstetten, Germany) or On-board Imager (Varian Medical Systems) allow a more accurate setup and verification before treatment. Integrating these new systems allows higher doses and greater-precision RT to be delivered into smaller volumes than conventional techniques. These elements are all integral parts of stereotactic ablative radiotherapy (SABR).

Key words

Carcinoma, non-small-cell lung; Lung neoplasms; Radiotherapy; Stereotaxic techniques; Survival rate

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In the early 1990s, Lax et al⁶ and Blomgren et al⁷ extrapolated the concept of stereotactic radiosurgery in the treatment of intracranial neoplasm to extracranial sites like liver and lung with encouraging results. The term 'stereotactic body radiotherapy' was coined to describe the precise delivery of radiation beams to body parts using a three-dimensional coordinated systems with reference to a fiducial marker that can be readily detected by imaging systems.⁸ Its synonym, stereotactic ablative body radiotherapy (SABR, pronounced as 'SAY-BER') has recently been advocated because the term 'ablation' can more accurately reflect the ultra-high radiation dose delivered in each fraction of radiation treatment, so as to overwhelm the normal cellular repair mechanisms and 'ablate' the tumour and adjacent tissues.⁹ The utilisation of SABR has bloomed in the past decade, but is still an evolving technique and more experience and clinical data are required.

In the Pamela Youde Nethersole Eastern Hospital, the SABR programme was established in June 2008, and by November 2011, 16 patients with early stage medically inoperable lung cancer were treated with this technique. This study aimed to evaluate treatment outcomes and safety of SABR in this population.

Methods

All 16 patients treated with SABR were considered to have inoperable disease either because of inadequate pulmonary reserve (the forced expiratory volume in 1 second being <1.5 L) or high surgical risks due to their pre-morbid status and concomitant illnesses. All patients had American Joint Committee on Cancer Stage I disease (7th ed) based on computed tomography (CT) of the thorax and abdomen and/or 18-fluorodeoxyglucose positron emission tomography (FDG-PET). Histological confirmation was also preferred but not mandatory.

Radiotherapy treatment planning and delivery

The planning and delivery of the high-dose, high-precision RT adhered to the recommendations of the European Organization for Research and Treatment of Cancer and the International Atomic Energy Agency.¹⁰⁻¹²

In brief, patients were immobilised by an alpha-cradle over the shoulders and back, with arms well-supported and holding a T-bar superior to the patient's head. Imaging and motion characterisation were performed by four-dimensional CT (4DCT; General Electric Medical System, Waukesha [WI], US). A reflective marker was placed on the abdomen of the patient, and the breathing pattern was video-monitored by the Varian Real-time Position Management System (Varian Medical Systems).

不適宜手術的早期肺癌病人接受立體定位放射治療：初期成效

目的 評核立體定位放射治療於不適宜手術的早期肺癌患者的初步成效及安全性。

設計 回顧病例系列研究。

安排 香港東區尤德夫人那打素醫院。

患者 自2008年開始所有接受立體定位放射治療的第一期非小細胞肺癌但不適宜手術的病人。

主要結果測量 病灶控制率、整體存活率和治療副作用。

結果 2008年6月至2011年11月期間，共16位第一期非小細胞肺癌病人接受立體定位放射治療。病人年齡中位數為82歲，以成人合併症評估27為標準，大部份（81%）病人都屬於中至高度合併症患者。研究追蹤期中位數為22個月，兩年病灶控制率達91%，而兩年整體及無疾病存活率分別為87%及71%，而治療並沒有引致等級三（美國國家癌症研究院不良事件常用術語標準）或以上的嚴重副作用。

結論 立體定位放射治療於不適宜手術之早期肺癌患者屬安全及有效。

Patients were instructed to breathe in a quiet and consistent manner. Once a regular breathing pattern was achieved, a contrast 4DCT with 2.5-mm slice thickness was obtained from the level of cricoid to the second lumbar vertebra; CT datasets for 10 phases spanning the respiratory cycles were then generated.

The gross tumour volume (GTV) was delineated in the 'pulmonary' window, with window width of 1600 and level of -600. The internal target volume (ITV) was derived by contouring the lesion in the maximum projection intensity dataset or by summation of the GTVs in all 10 breathing phases. The ITV was the same as the clinical target volume, ie, no microscopic margin was added. A margin of 8 mm was added to the ITV to form the planning target volume (PTV) so as to account for the setup errors and the intra-fractional movement.

A three-dimensional conformal RT technique was used. At least nine non-opposing fields were used to generate satisfactory treatment plans, and non-coplanar fields were used whenever indicated. The plan was normalised to the centre of the PTV. The dose was prescribed at 60 to 90% isodose level, and the appropriate prescription dose level was chosen where 95% PTV was covered by the prescription isodose and 99% PTV received at least 90% of the prescription dose. The planning criteria were similar to those published in the Radiation Therapy Oncology Group trial 0236.¹³

Treatment planning was performed using the Varian Eclipse treatment planning system (Varian Medical Systems). Dose calculation was performed using a Pencil Beam Algorithm (PCB) without tissue heterogeneity correction before June 2009, and was later changed to an Anisotropic Analytic Algorithm (AAA, version 8.6) with tissue heterogeneity correction.

Image-guided RT was employed to ensure high-precision delivery. Patients were set up with skin marks to start with, followed by on-board kilovoltage orthogonal imaging with the thoracic spine as the volumetric fiducial. Topographic images were then obtained by cone beam computed tomography (CBCT) and the tumour target itself served as the fiducial. Registration of the CBCT images to the planning of CT was performed, and automated to make corrections. The quality of the matching was crosschecked by clinical oncologists. 'Couch shift' was applied if the deviation in any direction was greater than 2 mm. The CBCT was repeated after treatment to assess the intra-fractional movement and for future setup margin modification, if indicated.

There were two different prescription dosages

to the PTV. For peripheral lesions that were located 2 cm in any direction beyond the proximal bronchial tree (including the trachea, carina, and major lobar bronchi), 60 Gray (Gy) in three fractions were delivered over 2 weeks for the PCB dose calculation algorithm and 54 Gy in three fractions for AAA. For centrally located lesions (within 2 cm from proximal bronchial tree), 50 Gy was given in five fractions over 2 weeks. Each fraction was delivered at least 48 hours apart. Thirty minutes before each treatment, patients received 4-mg dexamethasone to reduce the risk of radiation pneumonitis. A typical dose colour wash and its beam geometry are shown in Figure 1.

Patients were assessed for acute untoward effects 2 weeks post-SABR. They were then assessed clinically every 3 to 4 months in the first 2 years and then every 6 months thereafter. Whenever possible, a follow-up CT thorax was performed at the third-, sixth-, and twelfth-month post-SABR. Other relevant investigations were arranged at the discretion of the clinicians.

Controlled primary disease was defined as per the Green's criteria,^{11,14} which referred to the complete disappearance of all evidence of disease,

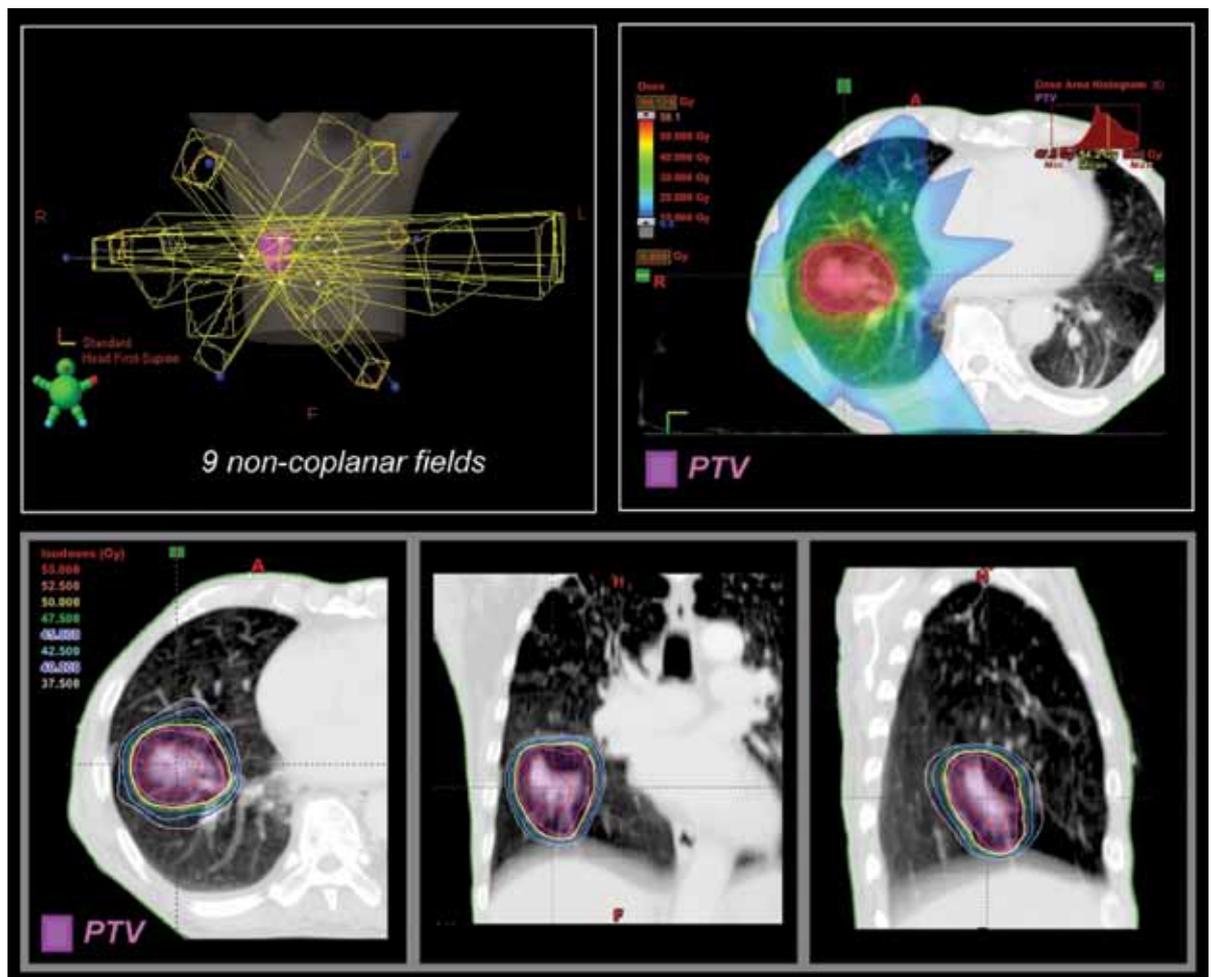


FIG 1. Typical beam geometry and dose colour wash of stereotactic ablative radiotherapy

or that the residual radiographic abnormalities assessed by thoracic CT at the third- or sixth-month post-RT had remained stable for another 6 months. If serial CT scans were not available, local failure was classified if more than 20% enlargement of the initial tumour was noted. Local-regional failure referred to the emergence of new lesions within the same lobe or occurrence of malignant hilar or mediastinal lymphadenopathy. Treatment-induced toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. Survival time was measured from the date of RT to the date of death or last assessment. Local control and survival rates were determined by the Kaplan-Meier method, using the Statistical Package for the Social Sciences (Windows version 15.0; SPSS Inc, Chicago [IL], US).

Results

From June 2008 to November 2011, 16 lung cancer patients were treated with SABR. Among patients still alive (n=14) in December 2011 (the cut-off month), the median follow-up time was 22 months. The baseline characteristics of these patients are listed in the Table. All except one had undergone tumour biopsy, and in two the biopsies did not yield a definitive diagnosis (due to inadequate amount of tissue).

One patient was lost to follow-up 30 months after SABR, and two were not assessed for their radiological response; one of the latter died before the first CT and the other was not yet due for the first imaging. Among the 14 assessed patients, one primary tumour failure and two local-regional recurrences were detected in two individuals. One patient had recurrent disease within the same lobe while the primary lesion was under control; the tumour was 33 mm and 60 Gy was delivered. The other patient achieved a partial response at the initial assessment but 11 months after completion of SABR, the primary tumour enlarged and metastasised to regional lymph nodes and pleura causing an ipsilateral pleural effusion. This was the only primary tumour failure and M1 disease noted to date; the patient had a 20-mm tumour to which 54 Gy was delivered. The remaining patients had controlled local disease as per Green's criteria. The estimated actuarial primary tumour control rate was 91% at 2 years.

Two cancer-unrelated deaths were also recorded. One patient with a history of acute myocardial infarction died of a recurrent cardiac infarct 82 days after SABR. The primary tumour was a left apical tumour and the cardiac dose was minimal (maximum point, 0.95 Gy and mean dose, 0.18 Gy). The other patient died 28 weeks after treatment. On her last admission, her chest radiograph revealed bilateral patchy infiltration, and the white cell count was mildly elevated. She was treated with antibiotics

TABLE. Patients and disease characteristics (n=16)

Patient/disease characteristic*	Data
Median age (range) [years]	82 (71-90)
Sex	
Male	11
Female	5
Smoking status	
Smokers/ex-smoker	13 (81%)
Never smoker	3 (19%)
Histology	
Adenocarcinoma	9 (56%)
Squamous cell	3 (19%)
NSCLC, NOS	1 (6%)
Not available†	3 (19%)
ACE27 index	
0/1	3 (19%)
2/3	13 (81%)
Performance status	
0/1	10 (63%)
≥2	6 (37%)
Median (range) forced expiratory volume in 1 second (L)	1.45 (0.38-2.05)
Median (range) tumour dimension (mm)	21.5 (11-38)
T stage distribution	
T1a	7 (44%)
T1b	3 (19%)
T2a	6 (37%)
Median (range) PTV volume (cc)	50 (18-96)
Metastatic workup modality	
CT scan	2 (13%)
PET-CT	14 (87%)
No. of lesions	
Peripheral lesion	12 (75%)
Central lesion	4 (25%)
Radiation dose fractionation	
50 Gy in 5 fractions over 2 weeks‡	4 (25%)
54 Gy in 3 fractions over 2 weeks‡	6 (38%)
60 Gy in 3 fractions over 2 weeks§	6 (38%)

* NSCLC, NOS denotes non-small-cell lung cancer (not otherwise specified), ACE27 Adult Comorbidity Evaluation 27, PTV planning target volume, CT computed tomography, and PET-CT positron emission tomography-computed tomography

† Biopsies of two patients were insufficient to reach pathological diagnosis; one patient refused biopsy, but serial CT images suggested lung cancer after multidisciplinary board assessment

‡ Dose calculated by Anisotropic Analytic Algorithm with tissue heterogeneity correction

§ Dose calculation by Pencil Beam Algorithm without tissue heterogeneity correction

but developed sudden arrest before undergoing thoracic CT for further evaluation; her preliminary diagnosis was pneumonia. Her last CT thorax (2 months prior to death) showed reduction in the size of the primary and no new lesions. The 2-year OS

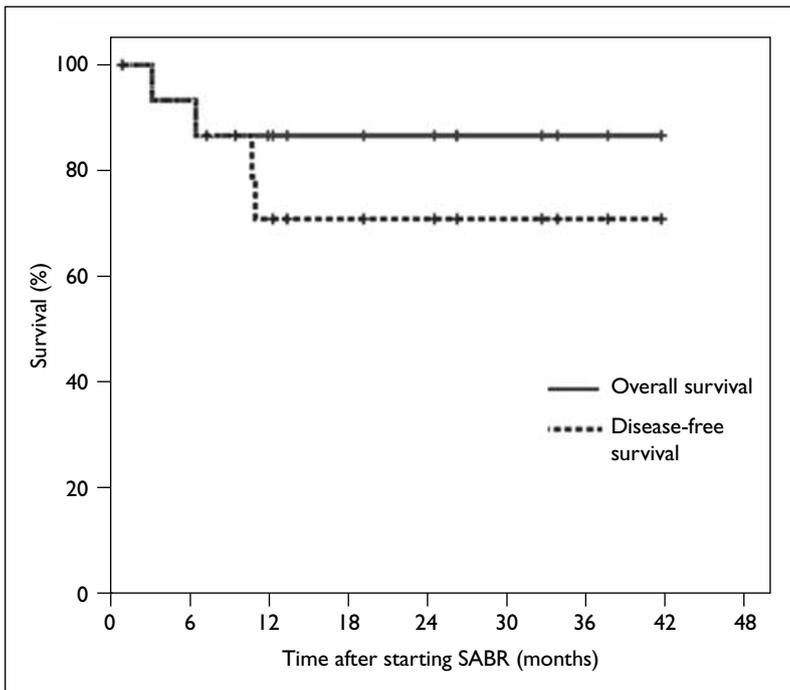


FIG 2. Overall and disease-free survival for the 16 medically inoperable patients with stage I lung cancer
SABR denotes stereotactic ablative radiotherapy

of the cohort was 87% and the 2-year disease-free survival was 71% (Fig 2).

The treatment toxicities were generally mild and transient. No severe (NCI-CTCAE ≥grade 3) pneumonitis was noted. One grade 2, acute, moist skin desquamation was detected 2 weeks post-SABR (Fig 3). No oesophagitis, chronic chest wall pain, or rib fractures were reported.



FIG 3. Transient wet desquamation 2 weeks after stereotactic body radiotherapy

Discussion

In this small case series, high rates of primary tumour control, disease-free survival, and OS with minimal side-effects were demonstrated. However, these results should be regarded as preliminary, due to the relatively short median follow-up (22 months) and limited number of patients. The high local control rate concurred with rates of 80 to 98% reported in other series.¹⁰ One local series by Ng et al¹⁵ also reported favourable local-regional control in 20 medically inoperable patients treated with hypofractionated stereotactic RT. Only three local-regional recurrences were detected after a median follow-up of 21 months. The 2-year disease-free survival was similar to ours (62% vs 71%). The median age of our cohort was 6 years older, but the 2-year OS was superior (87% vs 73%), and fewer distant metastases were found (1 vs 4). This could be due to differences in baseline medical conditions and the high percentage of our patient cohort staged by PET/CT (87%), while only CT thorax and abdomen were used for staging in the series by Ng et al.¹⁵ These favourable early outcomes provide further local evidence to convince surgeons and physicians that SABR is a safe and effective option for patients with early stage lung cancer, especially if they are too frail to undergo surgical resection.

Our current SABR programme offers many advantages over conventional RT. Radiobiologically, SABR gives a much higher biologically equivalent dose (BED) in an accelerated schedule. Higher BED and treatment acceleration has been shown to yield better survival outcomes.¹⁶⁻¹⁹ Technically, SABR incorporated improved immobilisation, image-guided RT and tumour motion characterisation by 4DCT. Individualised and tighter margins can be tailored, allowing higher doses to be delivered more precisely. In terms of dosimetry, multiple non-coplanar fields in SABR plans achieved higher conformity and more rapid isotropic dose fall off. The dose within the tumour was not uniform, with higher doses within the centre of the tumour where potentially hypoxic cells resided. Logistically, the number of treatment fractions were greatly reduced from the conventional 30-35 to 3-5, and the overall treatment period was shortened from 6-7 down to ≤2 weeks. This appeared especially favourable for frail elderly. From an economic perspective, SABR costs less than lobectomy, and appears to be more cost-effective than conventional RT.²⁰

Adult Comorbidity Evaluation 27 (ACE 27) is a commonly adopted co-morbidity assessment tool which grades 27 specific diseases into three different levels: mild (grade 1), moderate (grade 2), and severe (grade 3). Its prognostic role has been shown in various cancers.^{21,22} In all, 80% of the patients in our series had ACE 27 scores of 2 to 3. However, we still managed to

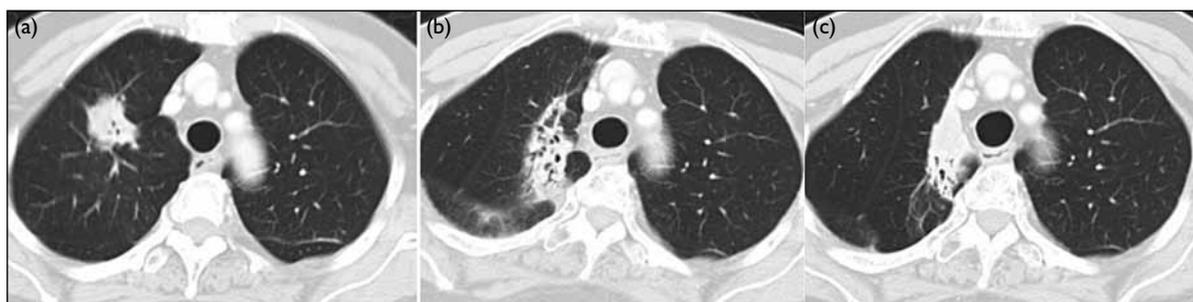


FIG 4. Tumour (a) before stereotactic ablative radiotherapy, the residual fibrosis, and contracture, and at (b) third-month and (c) 12-month post-treatment

treat them effectively with minimal toxicity. Patients with multiple medical illnesses are usually managed conservatively because of co-existing inoperable lung cancer. With SABR eradicating the life-limiting factor, the co-existing illnesses may then deserve more aggressive interventions, for instance, coronary angioplasty may be offered to patients with ischaemic heart disease.

Currently, international series have demonstrated encouraging results for SABR in early lung cancer treatment. However, there are no phase III results to confirm its superiority over conventional RT or surgery. A European trial, ROSEL (ClinicalTrials.gov ID NCT00687986), was conducted to randomise early stage lung cancer patients to undergo either surgery or SABR, but was abandoned due to poor recruitment. Though phase III data are absent, a Dutch population-based time-trend analysis demonstrated that with the introduction of SABR in Holland, the proportion of patients left untreated declined, there being a 16% absolute increase in RT usage, and OS improvement in the SABR-treated population.²³ In a Japanese multi-institution study, Onishi et al¹⁹ showed that survival rates in operable patients who received high BED (≥ 100 Gy) were excellent (88%) and appeared comparable to those of surgery.

Green's criteria were used to evaluate the treatment outcome in our series. It is known that SABR generates intense fibrosis and pneumonitis surrounding tumour tissue. Instead of a complete resolution of the tumour, varying degrees of residual fibrosis and contracture were often observed (Fig 4). Hence the terms complete or partial response as per RECIST (Response Evaluation Criteria in Solid

Tumors) could sometimes be arbitrary and observer-dependent. While definite outcome assessment relied on histological evaluation, serial scans appeared to be a more practical and non-invasive method for frail elderly. A supplementary PET scan could be especially helpful but costs could be a limiting factor. The natural history of the radiographic changes and functional imaging after SABR require further elucidation.

More clinical data are needed to address questions related to optimal dose fractionation, normal tissue constraints, applicability to more advanced stages of lung cancer etc. Improvements in technique and machines could further refine SABR. For instance, the use of volumetric-modulated arc therapy planning has been shown to significantly reduce the treatment time of SABR using conformal RT or intensity-modulated RT techniques.²⁴ Such improvement can reduce patient discomfort, minimise potential intrafractional movement, and maximise machine efficiency.

The SABR technique is still in the early stage of development in Hong Kong and still lacks publicity. This is reflected by the relatively small number of patients referred to our centre in the past 3 years. The low patient volume could hamper the training and development of SABR. These encouraging outcomes should be trumpeted in the community so that more suitable patients can benefit.

In conclusion, SABR can achieve high local control rates safely in medically inoperable patients with early lung cancer. The technique should therefore be introduced to suitable patients as a viable alternative.

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