

Non-surgical treatment of lung cancer: personalised stereotactic ablative radiotherapy

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ABSTRACT

Stereotactic ablative radiotherapy has emerged as a standard treatment for medically inoperable stage I non-small-cell lung cancer and selected cases of lung metastasis. Techniques to freeze or limit tumour movement during treatment and image-guided radiation delivery are integral to a successful stereotactic ablative treatment without overdose of surrounding normal structures. In this article, the practice in a local oncology institution will be used to illustrate the concept of personalised stereotactic ablative radiotherapy.

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Introduction

Lung cancer is the second most common cancer and number one killer among all cancers in Hong Kong.¹ Non-small-cell lung cancer (NSCLC) accounts for about 80% of all lung cancer cases. Surgery remains the mainstay of treatment for early-stage NSCLC. For patients who refuse or are medically unfit for surgery, stereotactic ablative radiotherapy (SABR) has emerged as a standard treatment. In the era of personalised medicine, SABR should be executed with techniques which are most suitable for the patient. In this article, the concepts of SABR, tumour motion control, and image-guided radiation delivery will be introduced. Then, using the Prince of Wales Hospital as an example, the approach to selecting the appropriate techniques for execution of personalised SABR will be explained.

Stereotactic ablative radiotherapy

Stereotactic ablative radiotherapy, also named as stereotactic body radiotherapy, is defined as “an external beam radiotherapy method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either a single dose or a small number of fractions”.² The goal of SABR is to give a very high (ablative) radiation dose to kill all cancer cells within the target while avoiding radiation damage to the surrounding normal tissues. For lung SABR, a radiation dose of 10 to 20 Gray (Gy, a radiation dose unit) per treatment fraction is delivered for a total of 48 to 60 Gy in five or less fractions within 2 weeks.

Indications for stereotactic ablative radiotherapy in lung cancer

Stage I non-small-cell lung cancer: medically inoperable disease or patient refuses surgery

Nowadays, SABR is the gold-standard treatment for patients with stage I NSCLC who refuse surgical intervention or are medically unfit to undergo surgery (mostly due to poor pulmonary function). Prospective phase I/II studies document local control rate of over 90% with SABR, with overall survival approaching that of surgery (Table 1³⁻¹⁰). In Hong Kong, the reported 2-year local control and 2-year overall survival rates were 89% to 95% and 53% to 87%, respectively.¹¹⁻¹³ Generally, SABR is well tolerated, even by patients with poor pulmonary function. Guckenberger et al¹⁴ demonstrated that SABR had only very limited acute and chronic pulmonary toxicity even in patients with poor pulmonary function and there was no requirement of minimal pulmonary function for safe practice of SABR.

In view of the encouraging data on local control and mild toxicity of SABR for medically inoperable cases, the gold-standard role of surgery for operable stage I NSCLC is now being challenged. At least two retrospective studies have shown that survival of patients with operable stage I NSCLC treated with SABR paralleled that of lobectomy.^{15,16} Another two prospective phase 2 trials reported 76% to 84% 2-to-3-year overall survival rates for operable stage I disease after SABR, which compares favourably to surgical outcomes.^{3,7} Unfortunately, all phase 3 trials

非手術治療肺腫瘤：個人化的立體定向消融放射療法

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立體定向消融放射治療已成為醫治患有第一期非小細胞肺癌但不適合做手術的病人及個別肺轉移個案的標準。凍結或限制腫瘤移動的技術和圖像引導放射治療是進行成功的立體定向消融治療不可或缺的元素，以避免周邊正常組織接受過高的電療劑量。本文會以本地一所腫瘤科醫院的臨床實踐說明個人化立體定向消融放射治療的概念。

comparing SABR with surgery in operable stage I NSCLC were terminated prematurely due to poor accrual. Thus, the race between SABR and surgery for the title of standard treatment for operable stage I NSCLC continues without a foreseeable end.

Oligometastasis involving the lungs with controlled primary tumour

Generally, oligometastasis is defined as one to five metastatic lesions besides the primary tumour. Evidence has emerged that patients with limited metastases can be cured by removal of all metastases. The reported 10- and 15-year survival rates of patients undergoing complete lung metastasectomy were 26% and 22%, respectively. Patients with fewer metastases and longer disease-free interval fared even better.¹⁷ Prospective studies of limited lung metastases treated with SABR reported 2-year local control and 2-year survival rates of 89% to 96% and 39% to 84%, respectively, which are not inferior to the surgical results.¹⁸⁻²¹

Stereotactic ablative radiotherapy versus conventional radiotherapy

The local control rate of stage I NSCLC after SABR is $\geq 90\%$, in contrast to 50% rate with conventional radiotherapy.²²⁻²⁴ A clinical dose-response curve of human malignant lung tumours has been established.²⁵ Thus, a high local tumour control can be achieved by delivering a high radiation dose. In lung cancer, however, the intrathoracic normal structures (normal lung tissues, spinal cord, brachial plexus, oesophagus, trachea and main bronchi, heart, great vessels, ribs and skin) close to the tumour may also receive a high radiation dose which may cause severe or even fatal treatment complications. It is this radiation damage of normal structures that limits the possible radiation dose to the lung tumour in conventional radiotherapy.

Stereotactic ablative radiotherapy is able to deliver a very high radiation dose to the target while sparing the surrounding normal tissues, thanks to its intrinsic physical advantage. On the other hand, many normal structures can tolerate a small volume of high-dose radiation without complications. Thus, we can deliver high-dose tumour radiation and yet limit volumes of the surrounding normal tissues exposed to high-dose radiation by reducing the size of the radiation field. In SABR, radiation field size reduction can be achieved through incorporation of techniques to limit tumour movement during radiotherapy (tumour motion management) and image-guided radiation delivery.

Physical property

Compared with conventional radiotherapy, SABR is able to create a very rapid dose fall-off at the

TABLE 1. Results of prospective studies of stereotactic ablative radiotherapy for early-stage non-small-cell lung cancer³⁻¹⁰

Study	No. of patients	Inclusion	Doses	Results
Timmerman et al, ³ 2013	26	T1-T3N0M0, operable	18 Gy x 3 fractions	2-Year LC 92% 2-Year OS 84%
Nagata et al, ⁴ 2012	100	T1N0M0, inoperable*	12 Gy x 4 fractions	3-Year OS 60%
Ricardi et al, ⁵ 2010	62	T1-T2N0M0, inoperable	15 Gy x 3 fractions	3-Year LC 88% 3-Year OS 57%
Timmerman et al, ⁶ 2010	55	T1-T2N0M0, inoperable	18 Gy x 3 fractions	3-Year LC 98% 3-Year OS 56%
Nagata et al, ⁷ 2010	64	T1N0M0, operable	12 Gy x 4 fractions	3-Year OS 76%
Fakiris et al, ⁸ 2009	70	T1-T2N0M0, inoperable	20 Gy (T1) - 22 Gy (T2) x 3 fractions	3-Year LC 88% 3-Year OS 43%
Baumann et al, ⁹ 2009	57	T1-T2N0, inoperable	15 Gy x 3 fractions	3-Year LC 92% 3-Year OS 60%
Nagata et al, ¹⁰ 2005	45	T1-T2N0M0, inoperable	12 Gy x 4 fractions	3-Year OS 83% (T1) - 72% (T2)

Abbreviations: LC = local control; OS = overall survival

* Inoperable means medically inoperable or patient refused surgery

target normal tissue interface so that radiation can be precisely delivered to the target without damaging the surrounding normal tissues. This can be achieved by aligning the treatment field borders or multi-leaf collimators close to the planning target volume (PTV) borders (refer to the “Individualised radiation target volume” section below for definition of PTV) and by prescribing dose at the part of the radiation dose depth curve with a steep slope, ie 60% to 90% isodose line. Such rapid dose fall-off property of SABR can be further enhanced by adoption of intensity-modulated radiotherapy or volumetric-modulated arc therapy techniques which, in addition, can create a concave radiation dose distribution to further improve radiation dose conformity to the target.

Tumour movement restriction during radiotherapy

A lung tumour will move with respiration. In conventional radiotherapy, the radiation field is enlarged to encompass the tumour in all respiratory phases. In SABR, however, tumour movement during radiotherapy is restricted by various tumour motion management techniques. As a result, the radiation field can be smaller, thereby, limiting the amount of normal tissues exposed to a high radiation dose.

Image-guided radiotherapy

Even with proper tumour motion management, there will be residual tumour movement both during the same treatment fraction (intra-fraction) and between different fractions on different days (inter-fractions). Therefore, daily pretreatment verification of tumour position by various image-guided radiotherapy (IGRT) techniques is essential to avoid geographical tumour miss. Radiation field size reduction can only be realised with IGRT.

Techniques to freeze or restrict movement of a lung tumour during stereotactic ablative radiotherapy

Active breathing control/voluntary inspiratory breath-hold

Breath-holding SABR can be achieved actively by active breathing control (ABC) or voluntarily by self-initiated breath-hold. The ABC apparatus is a modified spirometer consisting of two pairs of flow monitors and scissor valves to control inspiration and expiration, respectively. The operator activates ABC at a predefined lung volume by closing both valves to immobilise the breathing motion for 15 to 20 seconds. At the same time, radiation beam is switched on. Then, the patient is allowed to breathe freely until the next ABC activation. The cycle is repeated until complete delivery of a treatment fraction, which typically takes 30 minutes. Mostly,

ABC will be activated in inspiration when lungs expand, resulting in less normal lung irradiation (Fig 1a). A study showed that ABC reduced normal lung V20 (volume of normal lung tissues receiving a dose ≥ 20 Gy) by 34% compared with free breathing.²⁶ There is a good reproducibility of lung tumour position under ABC both inter-fractionally and intra-fractionally, with mean tumour displacement in supero-inferior direction of 1.1 mm and 0.3 mm, respectively.^{27,28} Voluntary inspiratory breath-hold technique is used in case a patient can hold his/her breath for at least 15 seconds but is unable to hold the mouthpiece of an ABC apparatus without air leakage.

Respiratory gating

Respiratory gating involves delivery of radiation only in certain phases of respiration. The gating window (respiratory phases at which radiation beam will be turned on) is usually selected at late expiratory

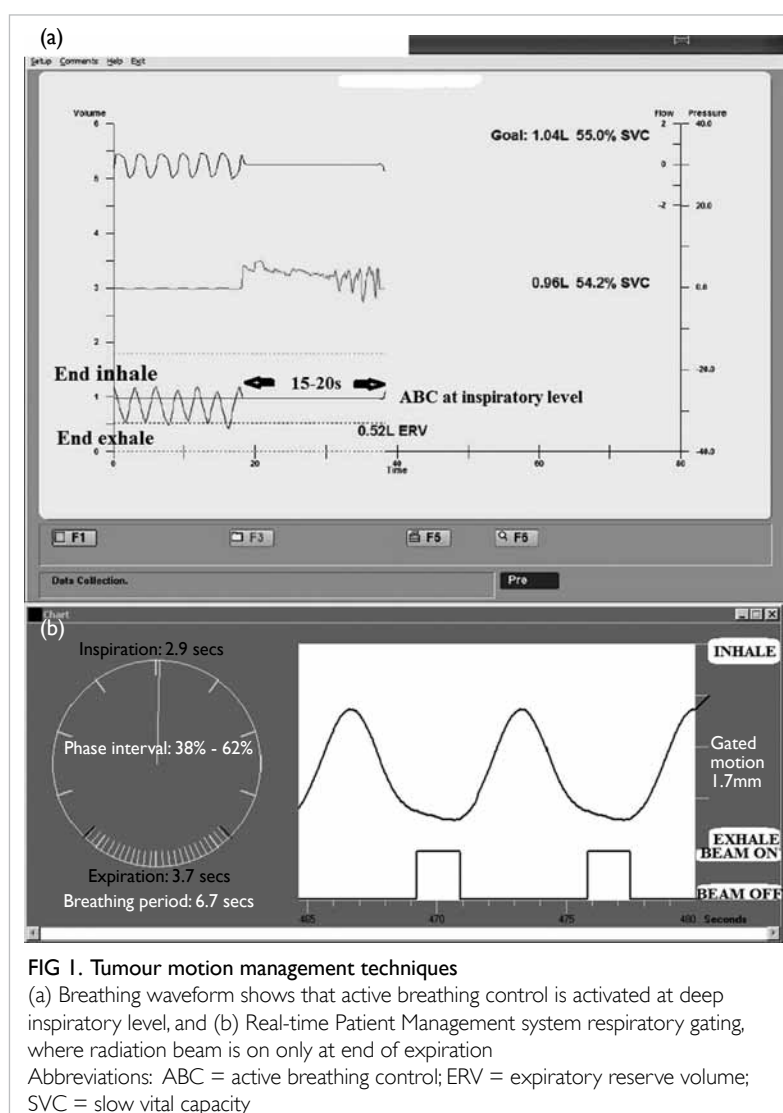


FIG 1. Tumour motion management techniques
 (a) Breathing waveform shows that active breathing control is activated at deep inspiratory level, and (b) Real-time Patient Management system respiratory gating, where radiation beam is on only at end of expiration
 Abbreviations: ABC = active breathing control; ERV = expiratory reserve volume; SVC = slow vital capacity

phases as a lung tumour stays for a longer period in the expiratory phase than in the inspiratory phase, resulting in a shorter treatment time. In addition, the tumour position will be more consistent and reproducible at end of expiration. A four-dimensional computed tomography (4D-CT; 4D means 3D + time) for radiotherapy planning purpose is done with the Real-time Patient Management (RPM) system (Varian Medical Systems, US), which consists of an infrared reflective block and an infrared tracking camera. The reflective block is placed on the anterior abdominal skin surface midway between the xiphisternum and umbilicus. The infrared camera tracks motion of the reflective block. The up-and-down breathing movement of the abdominal wall and thus position of the reflective block now reflects the respiratory phase during which a particular set of CT images are captured. As a result, positions of the tumour in various respiratory phases can be displayed on the 4D-CT images. A radiation field is designed according to the tumour positions at selected gating windows. Respiratory gating can be executed with either the RPM or the ExacTrac Adaptive Gating systems (Brainlab AG, Germany).

Real-time Patient Management system

During SABR, the infrared reflective block is placed on the patient’s abdominal wall and serves as an external indicator to predict the tumour location. The infrared camera will track movements of the reflective block to turn the radiation beam on (at gating window) and off (Fig 1b).

ExacTrac Adaptive Gating system

Similar to the RPM system, ExacTrac has an optical

infrared tracking system comprising several infrared reflective body markers (usually five to eight) and an infrared tracking camera mounted on the ceiling of the radiation treatment room (Fig 2a). The radiation beam will be turned on only at a predefined gating window. The advantages and disadvantages of different tumour motion management techniques are tabulated in Table 2.

Radiation delivery under image guidance

Multiple studies have concluded that neither external indicators (infrared reflective block in the RPM system^{29,30}) nor internal indicators (diaphragm,³¹ bony anatomy such as vertebral bodies^{32,33}) have a consistent correlation with tumour position over time. Therefore, direct visualisation of the lung tumour itself is required for accurate and precise radiation delivery. Image-guided radiotherapy is a procedure that uses various imaging techniques (eg X-ray and CT) to identify a tumour to guide the radiation beam during SABR treatment. It makes radiotherapy more accurate and causes less damage to healthy tissues.

Pretreatment verification of tumour position by a CT or X-ray imaging device mounted on a linear accelerator (Linac; a machine for generation and delivery of radiation beam) should be done daily for detection of inter-fractional tumour displacement, with necessary correction if there is significant tumour displacement from its planned position (Fig 3). Moreover, interval treatment verification with X-ray imaging during one treatment fraction is required for identification of intra-fractional tumour displacement.

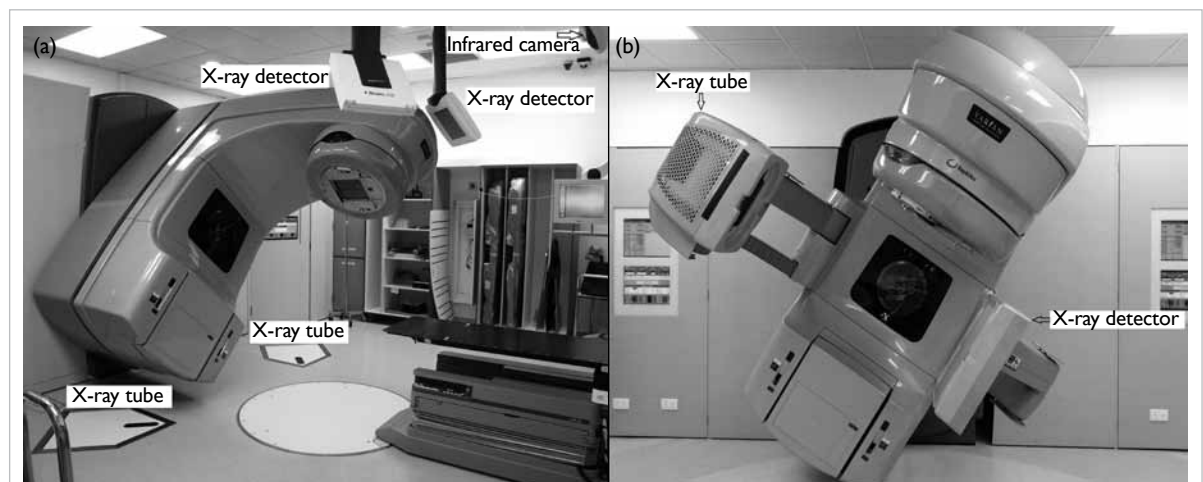


FIG 2. Image-guided radiotherapy facilities

(a) ExacTrac Adaptive Gating system. The two X-ray tubes are embedded on the room floor. The two amorphous silicon flat panel X-ray detectors, and the infrared tracking camera are mounted on the ceiling. (b) Onboard Imager. The X-ray tube and X-ray detector are mounted on the linear accelerator so that the X-ray tube-detector pair is always at 90° to the treatment head of the linear accelerator

TABLE 2. Comparison of different techniques

Technique	Advantage	Disadvantage
Tumour motion management technique		
Breath-holding	<ul style="list-style-type: none"> • Shorter treatment time • Smallest radiation target volume 	<ul style="list-style-type: none"> • Not applicable for patients with compromised pulmonary function • Causes discomfort to patients
Respiratory gating	<ul style="list-style-type: none"> • Feasible even for patients with compromised pulmonary function • Comfortable for patients 	<ul style="list-style-type: none"> • Long treatment time • Larger radiation target volume
Tumour Encompassing Targeting '3.5D' radiotherapy technique	<ul style="list-style-type: none"> • Shortest treatment time • Comfortable for patients 	<ul style="list-style-type: none"> • Largest radiation target volume • Not applicable if tumour excursion >1 cm
Image-guided radiotherapy technique		
Onboard Imager	<ul style="list-style-type: none"> • Useful for both breath-holding and respiratory gating techniques • Fluoroscopic mode available • Fiducial marker implantation not necessary 	<ul style="list-style-type: none"> • Less accurate • Cannot visualise small/obscure tumours • Unable to verify tumour position when radiation beam is on
Cone-beam CT	<ul style="list-style-type: none"> • Accurate • Can visualise the spatial relationship of tumour and surrounding normal tissues online • Fiducial marker implantation not required 	<ul style="list-style-type: none"> • Takes a long time for image acquisition, therefore not applicable for breath-holding technique • Four-dimensional cone-beam CT unavailable in most centres, therefore not applicable for respiratory gating technique • Unable to verify tumour position when radiation beam is on
ExacTrac Adaptive Gating system	<ul style="list-style-type: none"> • Can verify tumour position even when radiation beam is on 	<ul style="list-style-type: none"> • For respiratory gating only • Fiducial marker implantation necessary
Fiducial marker guidance	<ul style="list-style-type: none"> • Accurate 	<ul style="list-style-type: none"> • Risk of pneumothorax which may require chest drain for air drainage

Abbreviation: CT = computed tomography

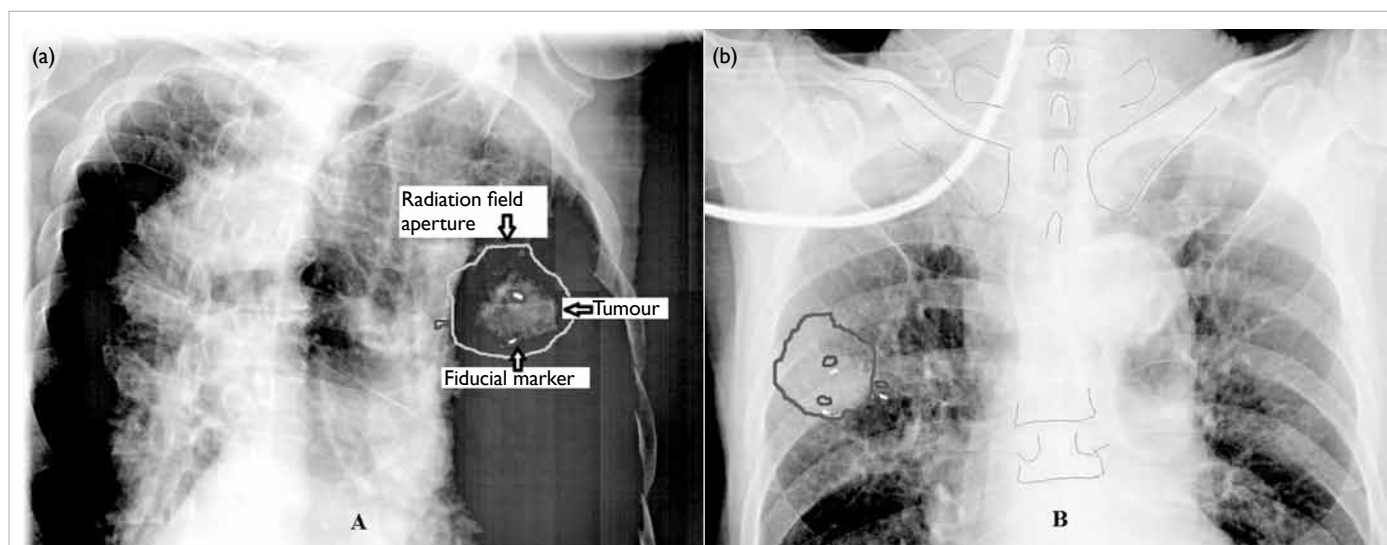


FIG 3. Pretreatment verification of tumour position. The small circles indicate the area where the fiducial marker is expected to stay during radiotherapy

(a) No displacement of the tumour. (b) Tumour displacement from its expected position, as indicated by displacement of the fiducial markers outside the small circles. The patient has to be repositioned for correction of tumour displacement before start of radiotherapy

Onboard Imager

Onboard Imager (OBI; Varian Medical Systems, US) is a high-resolution X-ray device mounted on the treatment head of a Linac to display real-time tumour location (Fig 2b). Radiographic images can be taken at the gating window for online (ie when a patient lies on treatment table of the Linac) verification of tumour position in RPM respiratory-

gated radiotherapy. In ABC treatment, the tumour position under ABC can also be verified online. It should be noted that X-ray images can be taken only when the radiation beam is turned off.

Cone-beam computed tomography

Cone-beam CT (CBCT) is a 3D mode of OBI, which is able to acquire and reconstruct 3D volumetric

data in one rotation of treatment head of the Linac in 1 minute. Because of the long image acquisition time, CBCT is unsuitable for treatment verification if breath-holding or respiratory gating techniques are used. Rather, it is a useful and accurate tool for daily treatment verification of the Tumour Encompassing Targeting radiotherapy.

ExacTrac Adaptive Gating

The ExacTrac Adaptive Gating system has two components: the optical infrared tracking system for respiratory gating (mentioned above) and the stereoscopic X-ray imaging system for online detection and correction of tumour position shift. The stereoscopic X-ray imaging system consists of two X-ray tubes embedded in the Linac room floor and two amorphous silicon flat panel detectors mounted on the ceiling; the angle between the two

X-ray tube-detector pairs is approximately 90° (Fig 2a). Stereoscopic X-ray can be taken at the gating window for verification of tumour position. Its advantage over OBI is that periodic X-ray acquisition at gating window is possible during both beam-on and beam-off periods. That means tumour displacement can be detected anytime during treatment, including during the beam-on period. Radiation beam can be turned off automatically if the tumour is displaced outside its allowed region. Table 2 compares the pros and cons of various IGRT techniques.

Personalised stereotactic ablative radiotherapy adapted to patient's needs and limitations

Individualised tumour motion management

The criteria for selection of an appropriate tumour motion management technique include (1) ability of the patient to tolerate inspiratory breath-hold for ≥15 seconds, (2) extent of tumour movement at tidal breathing, and (3) selected IGRT technique (refer to the 'Individualised image-guided radiotherapy' section below for details).

Ideally, all patients should be treated under breath-holding condition as the lung tumour will be frozen and a minimal safety margin is required for creation of a radiation field. In practice, many lung cancer patients are elderly and smokers with compromised pulmonary function. These patients cannot hold the breath long enough for SABR treatment. For patients unsuitable for breath-holding techniques, a 4D-CT is done under tidal breathing to assess the magnitude of tumour movement. If it is ≤1 cm, the Tumour Encompassing Targeting technique ('3.5D' radiotherapy) is used in which the radiation field will cover all possible tumour positions at any respiratory phase as shown on 4D-CT. For tumours with excessive (>1 cm) movement under tidal breathing, the respiratory gating technique should be utilised.

A flowchart showing the approach to selecting appropriate tumour motion management technique for lung SABR is shown in Figure 4a.

Individualised image-guided radiotherapy

An IGRT technique should be selected to match requirements of the selected tumour motion management technique and characteristics of the tumour (Fig 4b). A fiducial marker (a marker made of pure gold that can be visualised clearly on X-ray) can be implanted into or close to the tumour as an indicator of tumour location under OBI. There are various commercially available fiducial markers of different shapes and sizes, such as a cylindrical marker measuring 0.75 mm in diameter and 10 mm in length. Fiducial markers are implanted under CT guidance. In theory, all SABR treatments should be

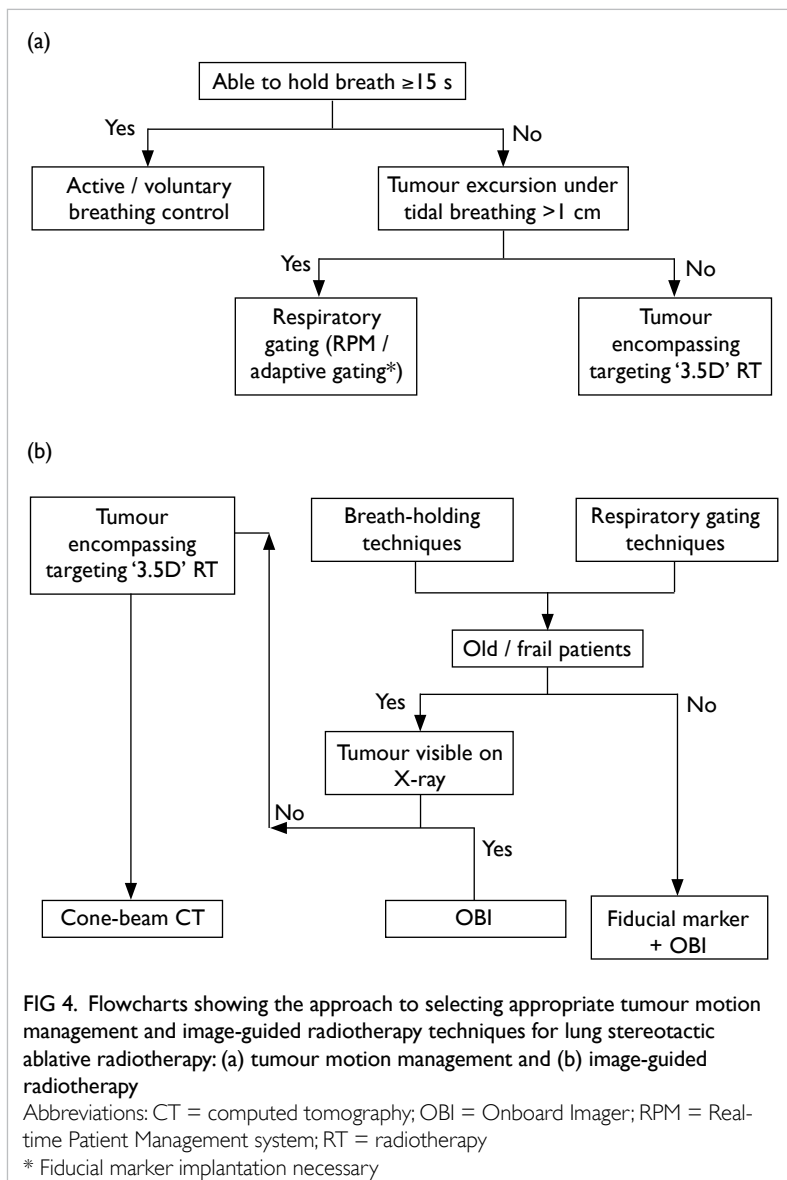


TABLE 3. Determination of target volumes in accordance with the selected tumour motion management and image-guided radiotherapy techniques

	ABC	Tumour encompassing targeting	RPM respiratory gating / adaptive gating
GTV	Tumour shown on CT done under ABC	Summation of GTV throughout entire 4D-CT data set	Summation of GTV within gating window (typically phases 40%-60% or 30%-70%)
CTV	= GTV	= GTV	= GTV
ITV	GTV + 3 mm	GTV +3 mm	GTV + 5 mm
PTV	<ul style="list-style-type: none"> • Fiducial marker / CBCT for setup • OBI for setup 		<ul style="list-style-type: none"> • ITV + 3 mm • ITV + 5 mm

Abbreviations: ABC = active breathing control; CBCT = cone-beam computed tomography; 4D-CT = 4-dimensional computed tomography; CTV = clinical target volume; GTV = gross tumour volume; ITV = internal target volume; OBI = Onboard Imager; PTV = planning target volume; RPM = Real-time Patient Management

executed either under fiducial markers guidance or with CBCT as these are the most accurate methods for pretreatment tumour position verification. In fact, CBCT is the IGRT technique of choice for '3.5D' radiotherapy. Nearly all patients cannot hold the breath long enough for performing CBCT, which typically takes a minute for 360° acquisition of a full set of CT images. Furthermore, 4D-CBCT is unavailable in most oncology centres in Hong Kong. As a result, CBCT pretreatment verification is impractical for both breath-holding and respiratory gating techniques. On the other hand, fiducial marker implantation under CT guidance will result in significant pneumothorax necessitating insertion of a chest drain. Thus, it is not recommended in old and/or frail patients. Provided that the tumour can be visualised on X-ray, OBI alone can be used for pretreatment verification in such patients. Unfortunately, a lung tumour may not be visible on X-ray because of its small size or close proximity to the ribs, mediastinum, or heart. If a fiducial marker is not implanted and the tumour is invisible on OBI, neither breath-holding nor respiratory-gated SABR treatment is realistic. Instead, the '3.5D' radiotherapy technique should be utilised with CBCT pretreatment verification.

Individualised radiation target volume

The International Commission on Radiation Units and Measurements Report 62 clearly defines various target volumes for radiation.³⁴ Gross tumour volume (GTV) is the tumour mass shown on clinical examination or by imaging. Clinical target volume (CTV) encompasses the subclinical microscopic disease around GTV. In SABR, the tissue immediately around GTV will receive a dose high enough to eradicate all possible microscopic disease. Therefore, CTV margin is not required in most of the cases, ie GTV = CTV. To compensate for possible inter-fractional and intra-fractional tumour movement, a further margin (internal margin [IM]) is added to CTV to create the internal target volume (ITV). As 4D-CT scan for radiotherapy planning

only delineates the snapshot tumour movement at the time of scanning, an IM is still required to allow for residual tumour movement. A final setup margin (SM) for all uncertainties in patient-radiation beam positioning during radiotherapy treatment is added to ITV to become the final PTV. The required IM and SM depend on the selected tumour motion management and IGRT techniques. As the breathing pattern of patients may change significantly both within one treatment and between different treatment sessions, a larger IM is indicated for respiratory gating techniques. Compared with fiducial markers and CBCT, OBI is less accurate for determination of tumour position during treatment, thereby, requiring a larger SM (Table 3).

Conclusion

Stereotactic ablative radiotherapy is the standard treatment for medically inoperable stage I NSCLC. Phase 3 trials are eagerly awaited to settle the debate on superiority of SABR or surgery in the treatment of operable stage I disease. Various tumour motion management and IGRT techniques are available for effective execution of SABR. Personalised SABR should be offered to suit each patient's needs and limitations.

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