Feasibility of intraoperative radiotherapy with X-rays for the treatment of superior sulcus tumours

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Research

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Abstract

Background Preoperative concurrent chemoradiotherapy (CCRT) followed by surgery has become the standard treatment for potentially resectable superior sulcus (SS) tumours. To date, intraoperative radiotherapy (IORT) for SS tumour treatment is primarily performed via brachytherapy; it achieves high local control, but has no influence on overall survival. Therefore, a novel therapy is required to increase the local control of SS tumours. The purpose of this study was to evaluate the feasibility and safety of IORT with low-energy X-rays for treating SS tumours. Methods Patients diagnosed with stage IIB-IIIA SS tumours with chest wall invasion and scheduled to undergo surgery were eligible for this prospective pilot study. Every patient was discussed at a lung cancer multidisciplinary team meeting. Patients with potentially resectable tumour were scheduled for neoadjuvant chemoradiotherapy followed by surgery, while those with resectable tumour were scheduled to receive surgery alone. Neoadjuvant chemotherapy consisted of two cycles of platinum-based doublet chemotherapy. Concurrent radiotherapy of 50 Gy in 25 fractions over 5 weeks was performed via intensity-modulated radiation therapy. IORT was administered to the tumour bed with close margin. The primary endpoint was acute toxicity and secondary endpoints were late spinal cord and brachial plexus toxicity. Results Between August 22, 2014 and November 30, 2017, we enrolled nine patients (seven males and two females). Anaemia was the most common acute complication, with grade 3 anaemia occurring in three patients who received preoperative CCRT. Other side effects included pneumonia (1 patient), prolonged air leakage (1), and grade 1 brachial plexus injury (1). The average follow-up period was 29.4 (range; 13.3-50.4) months. All patients are alive. Distant metastasis was observed in two patients, one with contralateral lung metastasis and another with pericardial metastasis. Conclusions IORT with low-energy X-rays is a technically feasible and relatively safe treatment modality for patients with superior pulmonary sulcus tumours.

Background

Preoperative concurrent chemoradiotherapy (CCRT) followed bysurgery has become the standard of care for potentially resectablesuperior sulcus (SS) tumours, owing to the promising results of twoprospective multi-institutional randomised phase II trials(Southwest Oncology Group 9416 [2007][1] and Japan Clinical Oncology Group 9806[2008][2]). Thefive-year overall survival (OS) of patients treated in this mannerwas reported to be 40–60%,[1–3] and compared to inductionradiotherapy alone, neoadjuvant CCRT decreased the incidence oflocal relapse from 40–12%.[1] In order to decrease local failure ratesand ultimately improve OS, intraoperative radiotherapy (IORT) wasexplored as a treatment for SS tumours. IORT has been primarilyperformed via brachytherapy, which delivers a highly localised doseof radiation to tumours while sparing adjacent normal tissue. Inbrachytherapy, radioactive seeds are permanently implanted intotumours with the help of image guidance. Moreover, studies havereported that brachytherapy achieves high local control in selectedpatients with SS tumours.[4–6] However, intraoperativebrachytherapy combined with perioperative radiotherapy has had noinfluence on OS or regional control when complete resection isachieved, as noted in the Ginsberg et al study,[6] the largest retrospective IORTstudy to date, which included 102 patients treated withbrachytherapy. The value of

intraoperative brachytherapy inpatients with complete resection remains in question. Therefore, anovel therapy is required to increase the local control of SStumours. The purpose of this pilot study was to assess thefeasibility and safety of IORT with low-energy X-rays for thetreatment of SS tumours.

Methods

Study Design

This was a single-arm prospective study. To assess thefeasibility of IORT with low-energy X-rays for treating SS tumours,our primary endpoint was acute toxicity and our secondary endpointswere late spinal cord and brachial plexus toxicity. All proceduresin this report were performed in accordance with the ethicalstandards of the Guangdong Provincial People's Hospital ethicalcommittee and the 1964 declaration of Helsinki and its lateramendments or comparable ethical standards. Approval for conductingthis study was granted by the Medical technical Committee and theInstitutional Review Board (2016367A). Written informed consent wasobtained from each patient prior to participation.

Patient Eligibility

Patients with previously untreated locally advanced SS tumourswere prospectively enrolled in this study. The patient eligibilitycriteria were as follows: histologically confirmed non-small celllung cancer; tumour located in the apex of the lung with chest wallinvasion; diagnosis of clinical stage II-III tumours according tothe American Joint Committee of Cancer (seventh edition);age > 18 years; eligible for surgery; and with an EasternCooperative Oncology Group performance score of 0–1; close surgicalmargins. The exclusion criteria were as follows: clinicalmulti-station or bulky N2 or N3 disease; distant metastasis;malignant effusion; pleural dissemination; previous thoracicradiotherapy; pregnancy; and refusal to undergo surgery.

Treatment

A flow-chart of patient care and the numbers of patients treatedat each time point in the study is shown in Fig. 1. All patients were evaluatedduring a lung cancer multidisciplinary team (MDT) meeting todiscuss their treatment. The decision to administer neoadjuvanttreatment depended on the evaluation of resectability and thepatient's choice. If the tumour was technically resectable, surgerywas performed without neoadjuvant treatment. The neoadjuvantchemotherapy regimen for patients with potentially resectabletumour was two cycles of platinum-based doublet regimen, consistingof cisplatin (50 mg/m^2 d1, 8) and etoposide(50 mg/m^2 d1-5) for concurrent chemotherapy, anddocetaxel (120 mg/m^2 d1) and cisplatin(50 mg/m^2 d1) for induction chemotherapy.Radiotherapy, with a dose of 50 Gy/25 fractions/5 weeks, wasperformed via intensity-modulated radiation therapy (IMRT) with anenergy of 6 MV. Patient evaluations were performed after four weeksof neoadjuvant treatment via positron emission tomography-computedtomography (PET-CT) or computed tomography (CT). Video-assistedthoracoscopic surgery (VATS) lobectomy with systematic mediastinallymphadenectomy was performed for all patients.

IORT was administered to the tumour bed via the PRS400 PhotonRadiosurgery System (Carl Zeiss, Germany), also called theIntrabeam system, when surgical margin status was defined by thesurgeon as close margins, as these can cause a high risk ofrelapse. The Intrabeam system is a miniature, high-dose rate andlow energy X-ray (50 kV) source which emits photon radiationdirectly to a tumour or tumour bed. The dose rate at the surface ofapplicators is related to the size of the applicator. A set ofrigid reusable spherical applicators is available with diametersranging from 1.5 to 5.0 cm. The maximum length of tumour bedwas measured after resection by the surgeon. The tumour bed on thechest wall was delineated on preoperative CT scans by a radiationoncologist and regarded as a curved surface, thus the diameter ofapplicator was calculated by the formula: diameter = 360 • arclength ÷ [π• central angle (degrees)] (Fig. 2). A radiation dose wasspecified at the reference point at a distance of 0.5-1.0 cmfrom the applicator surface, which was determined based on thedistance to adjacent critical organs. The applicator was positionedin direct contact with the target tissue. Figure 3 illustrates an anatomicaldiagram of the Intrabeam system technique in patients with SStumour. Equivalent dose in 2-Gy fractions (EQD2) was calculated forthe EBRT and IORT course according to the linear-quadratic model,using an α/β value of 2 Gy for spinal cord and brachialplexus. The maximum point dose to the spinal cord or brachialplexus was limited to 50 $Gy_{2/2}$.

After IORT, surgical clips were placed in the radiation field tomark the IORT area on CT scans. Postoperative CT was then performedafter extubation. The postoperative CT images were transferred toEclipse TPS and subsequently fused with the correspondingpreoperative CT images, in order to calculate and evaluate dosedistribution and the radiation dose of organs at risk (OAR).

Follow-up

Follow-up monitoring was implemented at 4 and 12 weeks aftersurgery, then every three months during the first two years, andevery six months for another three years. During these follow-ups,acute toxicity was evaluated within three months after surgery,whereas late toxicity was evaluated from three months aftertreatment. Both a thoracic surgeon and radiation oncologistassessed acute and late toxicity in accordance with version 4.0 ofthe National Cancer Institute's Common Toxicity Criteria forAdverse Events (NCI-CTCAE 4.0) at the date of each follow-upvisit.

For our literature review, we performed an extensive search ofboth the PubMed and Medline databases in December 2018 using thefollowing search terms: "superior sulcus tumour", "apical lungcancer", and "intraoperative radiotherapy".

Results

A total of nine treatment-naive patients (seven males and twofemales) with clinical stage II-III SS tumours were enrolled inthis pilot study between August 22, 2014 and November 30, 2017. Thepatients' clinical features and treatment details are presented inTable 1. Two of the ninepatients were evaluated to be resectable at baseline by the MDT,and received surgery without neoadjuvant treatment. One of theother

seven patients refused radiotherapy and received neoadjuvantchemotherapy alone. Of these nine patients, six underwentlobectomy, chest wall resection and systemic lymph node dissectionvia VATS, and three underwent lobectomy and systemic lymph nodedissection. Of these three, two underwent lobectomy because theirtumours greatly regressed after neoadjuvant treatment, as indicatedby the fluorodeoxyglucose F18 uptake seen on their post-neoadjuvanttreatment PET-CT images, and the fact that no tumour cells werefound during intraoperative frozen section analysis. In the thirdpatient, chest wall invasion was suspected on preoperative images,and during surgery, we saw that the patient's tumour actuallyinfiltrated the parietal pleura without rib invasion. We were ableto have it completely excised and the resection margin was negativeon intraoperative frozen section diagnosis. Therefore, chest wallresection was no longer considered necessary in these three cases.Postoperative histopathology confirmed complete (R0) resection inall patients. A radiation dose of 6.5-8.0 Gy at a distance of0.5-1 cm from the applicator's surface was delivered to allpatients during surgery.

Anaemia was the most common acute complication observed, withgrade 3 anaemia (Haemoglobin < 8.0 g/dL) occurring in threepatients who underwent preoperative CCRT. Additionally, one patientdeveloped a fever of over 39°C at six hours post-surgery, indicatingpulmonary infection. After this patient underwent four days ofantibiotic therapy, the patient's body temperature dropped back tonormal. Another patient had a prolonged air leak after theoperation, which was successfully treated on the 12th postoperativeday. This patient was discharged three days after his postoperativethoracic CT scan revealed leakage resolution. One patient had grade1 brachial plexus injury with right shoulder numbness. Radiationmyelopathy, wound dehiscence or infection, pulmonary andbronchopleural fistulae, empyema, cardiac failure, and respiratoryfailure were not observed during the study period. Each patients'postoperative complications are listed in Table 2.

The average postoperative length of hospital stay was 8.7 days(range, 4–15 days). All patients were alive during the averagefollow-up period of 29.4 months (range, 13.3–50.4 months). Themedian disease-free survival period was 28.3 months. During thefollow-up period, distant metastasis was observed in two patients.Of these two patients, one suffered from single contralateral lungmetastasis at 11 months post-surgery, so this patient receivedradiofrequency ablation. The other had multiple mediastinal lymphnode and pericardial metastasis, so this patient receivedchemotherapy. Figure 4 showsthe swimmer survival plot of patients in our study.

Discussion

Owing to the presence of adjacent critical organs, it isdifficult to achieve microscopic radical resection for SS tumours.However, rationally speaking, an approach that includes an IORTmodality which delivers the maximal therapeutic dose of radiationto tumour beds, while also minimising radiation exposure tosurrounding normal tissue, would kill residual microscopic lesionsafter resection. In previous studies, high local control of SStumours were achieved in treatment modalities which included IORT(Table 3).

In our study, IORT with low-energy X-rays was performedsuccessfully and safely in all nine SS tumour patients. No in-fieldrecurrence was observed, and the longest follow-up period was overfour years. Moreover, it achieved high local control in patientswith a high risk of local relapse. Severe anaemia (≥ Grade 3), themost common acute toxicity-related complication seen in our study,was observed in patients who received preoperative CCRT. This mayhave been due to the inability of the patients' hematopoieticsystems to recover from induction CCRT. The other side effectsobserved in our study were mild. Notably, in a study byMartinez-Monge et al,[5] 17/18patients with SS tumours were treated with preoperative CCRTfollowed by surgery and intraoperative electronic radiotherapy(IOERT). Patients in this study had a local failure rate of 9.0%with a median follow-up period of > 24 months. However, twoof their patients died as a result of complications, and theirtreatment-related morbidity was high. Additionally, thepostoperative lengths of hospital stay in our study were a littlelonger than those in a previously published report,[7] as we had patients scheduled to undergo CTafter extubation, which took three to four postoperative days.Furthermore, the chest wall was conserved in three patients due tothe tumour-free margins observed during the intraoperative frozensection analysis and IORT applied to tumour beds in our study.

Until now, the clinical experiences of IORT in treating SStumours have been based on IOERT and brachytherapy. Seed migration,lack of radiological protection, and limited patienttransportability during operations are all obstacles associatedwith brachytherapy and IOERT. The Intrabeam system, a new mobileIORT system, has several advantages over brachytherapy and IOERT.Firstly, the relative biological effectiveness of the Intrabeamsystem's low-energy X-rays is higher than 192-Ir.[8] Secondly, the Intrabeam system's radiationdose is limited to a small volume, due to the X-rays' rapid dosefall-off of 50 kv, which protects normal surrounding tissue.Thirdly, the Intrabeam system can be administered in a standardoperating room and moved between different operating rooms, whichis not possible during IOERT. Finally, the X-ray source of theIntrabeam system is placed in a mobile arm, which holds theapplicator in the desired position. Furthermore, implementing IORTwith the Intrabeam system has been used for treating many types ofcancer, including breast cancer,[9] brain tumours,[10] and head and neck cancer,[11] as described in previously publishedstudies. These physical and radiobiological advantages make IORTwith the Intrabeam system a potentially more effective option fortreating SS tumours than IORT with brachytherapy and IOERT.However, a disadvantage of the Intrabeam system is that the maximumdiameter of the spherical applicator is 5 cm, which can limitthe radiation field.

Our study has several limitations. First, the dose distributionof IORT was estimated via preoperative and postoperative CT and,therefore, may be inaccurate because of the differences betweenpreoperative and intraoperative positions. Intraoperative imagesare needed to acquire a more accurate dose distribution. Second,our sample size was very small. Further studies with larger studypopulations are required to fully confirm the safety and efficacyof this procedure.

Conclusions

Our research has significant clinical applicability, as thisreport presents the first patients to receive low-energy X-rayintraoperative radiation for the treatment of SS tumours. Moreover,our results also suggest that this method can achieve high localcontrol. IORT with the Intrabeam system is a technically feasibleand relatively safe treatment modality for patients with superiorpulmonary sulcus tumours.

List Of Abbreviations

CCRT, concurrent chemoradiotherapy; IORT, intraoperative radiotherapy; SS, superior sulcus; NSCLC, non-small cell lung carcinoma; IMRT, intensity modulated radiation therapy; EP, etoposide/cisplatin; VATS, video-assisted thoracoscopic surgery; OAR, organs at risk; IOERT, intraoperative electronic radiotherapy; OS, overall survival; PET-CT, positron emission tomography-computed tomography; CT, computed tomography

Declarations

Ethics approval and consent to participate

This study was approved by the Medical technical Committee and the Institutional Review Board (2016367A). Written informed consent was obtained from each patient prior to participation.

Consent for publication

Not applicable due to absence of any personal or individual data in the present publication.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

YP, XNY, WZZ and YLW designed and directed the project. ZYC, YL, RQL, SD and SXX was responsible for the treatment and clinical care of the patients. QYH collected the data. YP and YLW contributed to manuscript writing, critical review and editing of the paper. All authors have read and approved the final manuscript.

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Tables

Table 1. Clinical features and treatment details of six cases

Cases	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age (y)	56	49	70	51	66	58	61	60	67
Gender	M	M	M	M	M	M	F	M	F
Clinical presentation	Cough and weight loss 10 kg for 1 month	Left shoulder pain for 1 month	Right shoulder pain for 1 month	Right shoulder pain for 1 week	No symptom	Cough for 1 month	Cough and hemoptysis for 1 month	Left shoulder pain for 2 years	No symptom
Histology	SCC	SCC	Adeno	Adeno	SCC	SCC	SCC	Adeno	Adeno
PS	1	1	1	1	0	1	1	1	0
Clinical Stage	cT3N0M0	cT3N1M0	cT3N2M0	cT3N0M0	cT4N0M0	cT4N0M0	cT3N1M0	cT3N0M0	cT3N0M0
Location of tumour	Anterior	Posterior	Posterior	Posterior	Anterior	Anterior	Anterior	Posterior	Posterior
Smoking (Pack/year)	None	30	80	60	None	60	None	None	None
Pre-treatment	Chemo	CCRT	CCRT	-	CCRT	CCRT	CCRT		CCRT
Tumour response	PR (-30%)	PR (-30%)	PR (-40%)	-	PR (-43%)	CR	SD (-20%)		SD (-26%)
Surgery	Lobectomy + rib 2^{nd}	Lobectomy + rib $2^{nd}3^{rd}$	Lobectomy + rib $3^{rd}4^{th}$	Lobectomy	Lobectomy	Lobectomy	Lobectomy + rib $1^{nd}2^{nd}$	Lobectomy + rib 2^{nd}	Lobectomy + rib 3^{rd}
Completeness of resection	R0	R0	R0	R0	R0	R0	R0	R0	R0
Size of applicator (cm)	3	4	5	4	4	4	3.5	5	4.5
Pathological Stage	pT2N0M0	pT3N0M0	pT3N0M0	pT3N0M0	pTisN0M0	pTxN0M0	pT3N0M0	pT3N0M0	pT3N2M0

IORT									
Radiation dose (prescription depth)	8.0 Gy (0.5 cm)	6.5Gy (1.0 cm)	8.0 Gy (1.0 cm)	8.0 Gy (0.5 cm)	6.5 Gy (0.5 cm)	6.5 Gy (0.5 cm)	6.5 Gy (0.5 cm)	6.5 Gy (0.5 cm)	6.5 Gy (0.5 cm)
Surface dose (Gy)	15.7	22.2	22.7	15.8	12.8	12.8	12.2	11.6	12.1
Radiationtime (min)	19.9	30.7	57.6	22.0	17.3	17.3	15.0	29.0	22.0
DFS (m)	50.4	35.4	33.1	29.7	28.3	7.8	19.8	14.7	13.3
Survival (m)	50.4	35.4	33.1	29.7	28.3	22.3	21.1	14.7	13.3

*M: male; F: female; SCC: squamous cell carcinoma; Adeno: adenocarcinoma; PS: performance status; Chemo: chemotherapy; CCRT: concurrent chemoradiotherapy; PR: partial response; CR: complete response; SD: stable disease; R0: complete resection; IORT: intraoperative radiotherapy; DFS: disease-free survival

Table 2. Postoperative complications in all cases

Patients	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Postoperative hospital stay (d)	7	8	15	6	5	15	4	8	7
Bleeding (ml)	300	200	1000	100	250	200	150	200	100
Anaemia	2	2	3	1	0	3	2	0	1
Neutropenia	0	0	2	0	0	0	2	0	2
Thrombocytopenia	0	0	0	0	0	0	0	0	0
Pneumonia	0	0	0	0	0	0	0	0	2
Postoperative haemorrhage	1	1	1	1	1	1	1	1	1
Prolonged air leak	None	None	Yes	None	None	None	None	None	None
The delay in removing the chest drain	None	None	Yes	None	None	None	None	None	None

Table 3. Cases of SS tumours treated with IORT in the English literature

Authors	No.	IORT	Treatment (No.)	Outcome
Ginsberg et al. (1994) [5]	100	Brachytherapy	EBRT	5 y OS: 26% (all); IORT+R0 resection: NS; IORT+R1, R2 resection: 9%
Martinez-Monge et al. (1994) [6]	18	IOERT 6-18 Mev 10-15 Gy	C+CCRT+S+IORT(15) CCRT+S+IORT (2) CCRT (1)	m follow-up: 24+ m 4 y OS:56.2% 4 y LC: 91%
Ohta et al.(2001) [7]	2	Brachytherapy 192 Ir (21 Gy and 30 Gy)	C+S+IORT (1) S+IORT (1)	Follow-up: 6 m and 10 m No recurrence
Van Geel et al. (2003) [4]	26	Brachytherapy 192 Ir (10 Gy)	EBRT (3) EBRT+S (2) EBRT+S+IORT (21)	median follow-up:18 m median OS: 14 m LC: 85%
Torre et al. (2009) [8]	24	Brachytherapy 192 Ir (10 Gy)	C+S (18) CCRT+S (15) IORT (7)	5 y OS: 56.6% IORT: NS

IORT: intraoperative radiotherapy; No: number; C: chemotherapy; EBRT: external beam radiotherapy; CCRT: concurrent chemoradiotherapy; S: surgery; IOERT: intraoperative electronic radiotherapy; OS: overall survival; LC: local control; NS: not significant

Figures

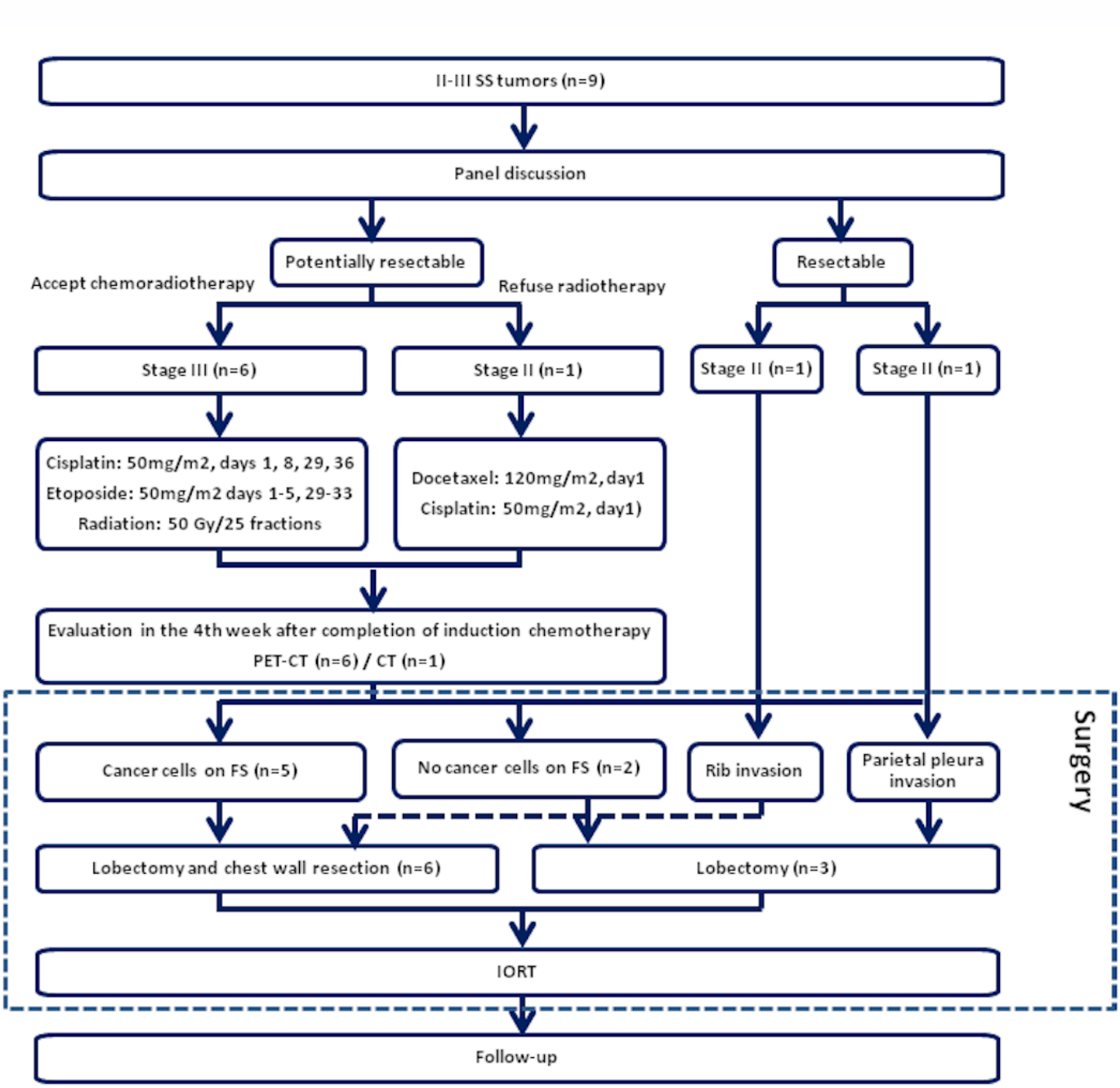

Figure 1

Flow chart of patient care and the numbers of patients treated at each time point. SS, Superior sulcus; Chemo, chemotherapy; CCRT, concurrent chemoradiotherapy; FS, frozen section; IORT, intraoperative radiotherapy

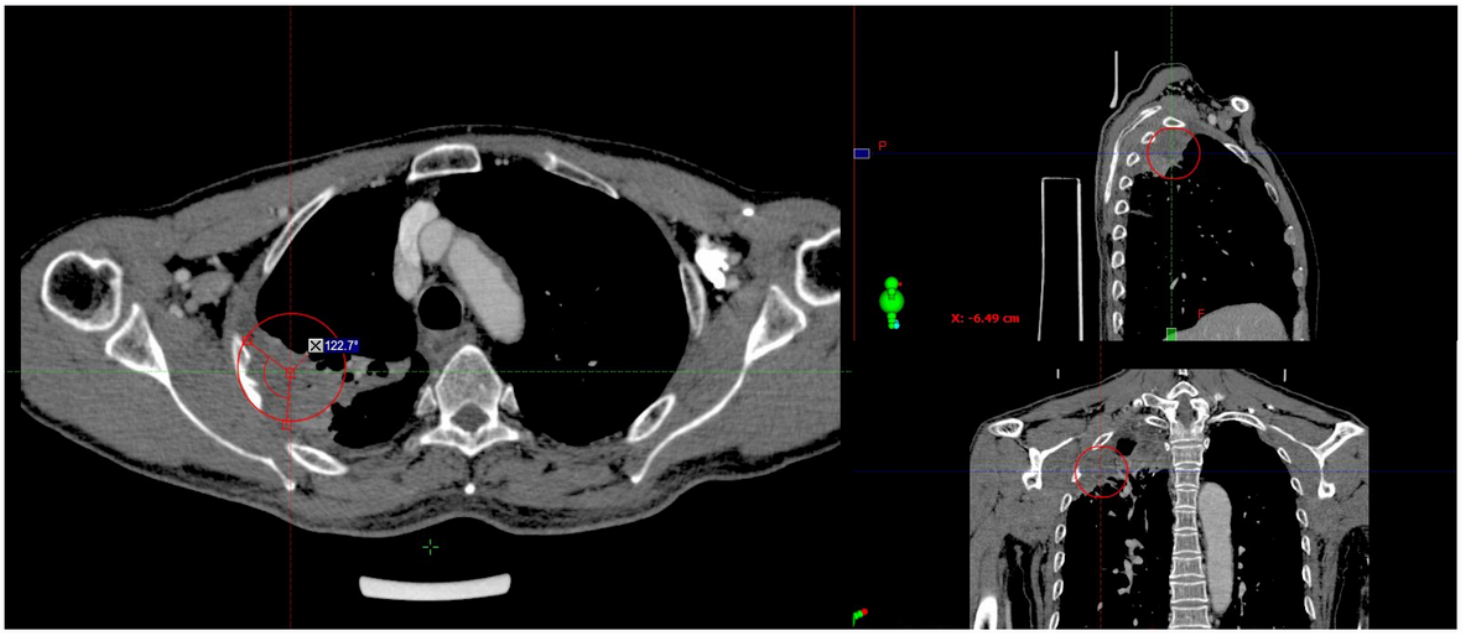

Figure 2

Calculation of the diameter of the applicator on preoperative CT scan

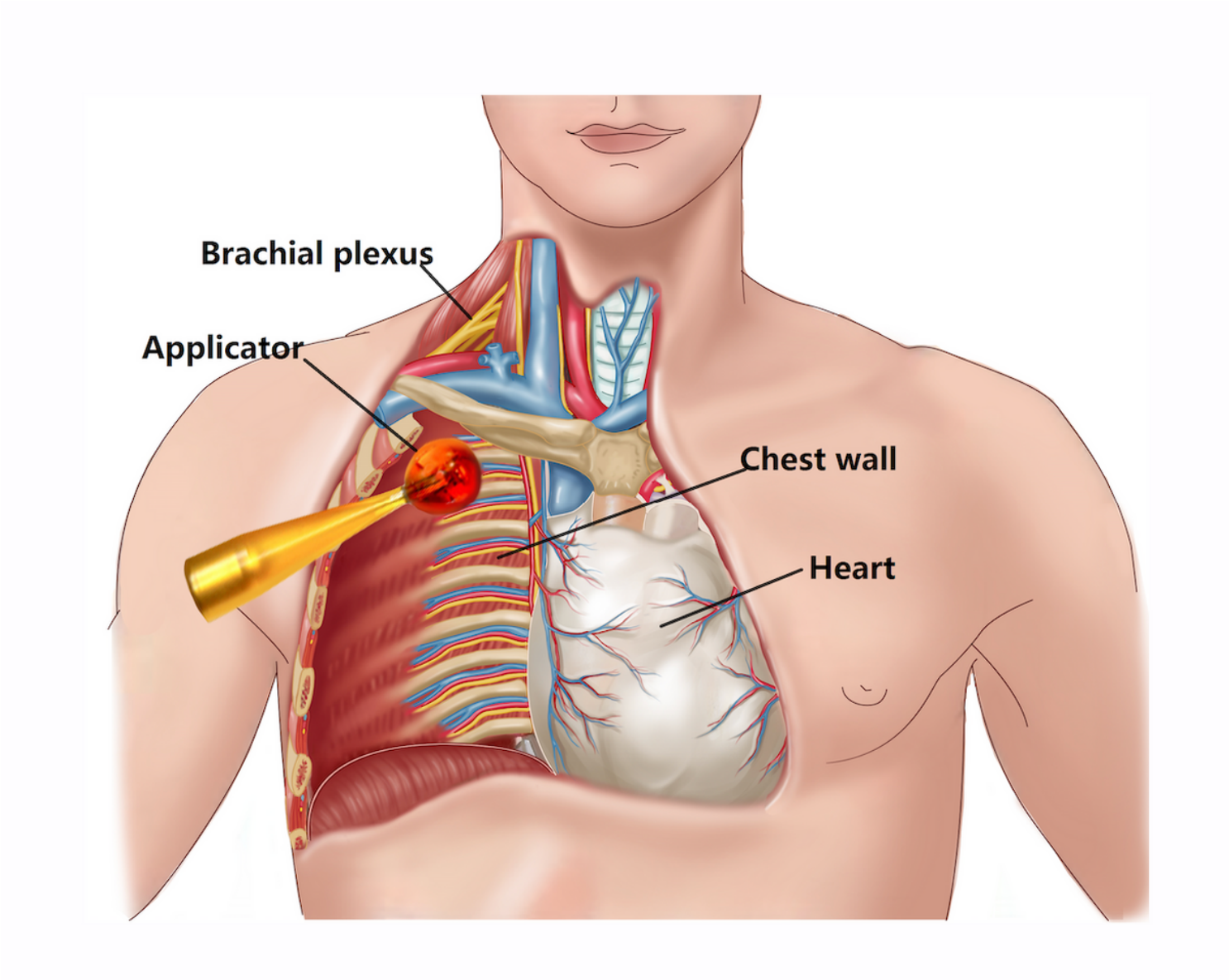

Figure 3

An anatomical diagram of the Intrabeam system technique. This figure shows an Intrabeam applicator being placed in the tumour bed.

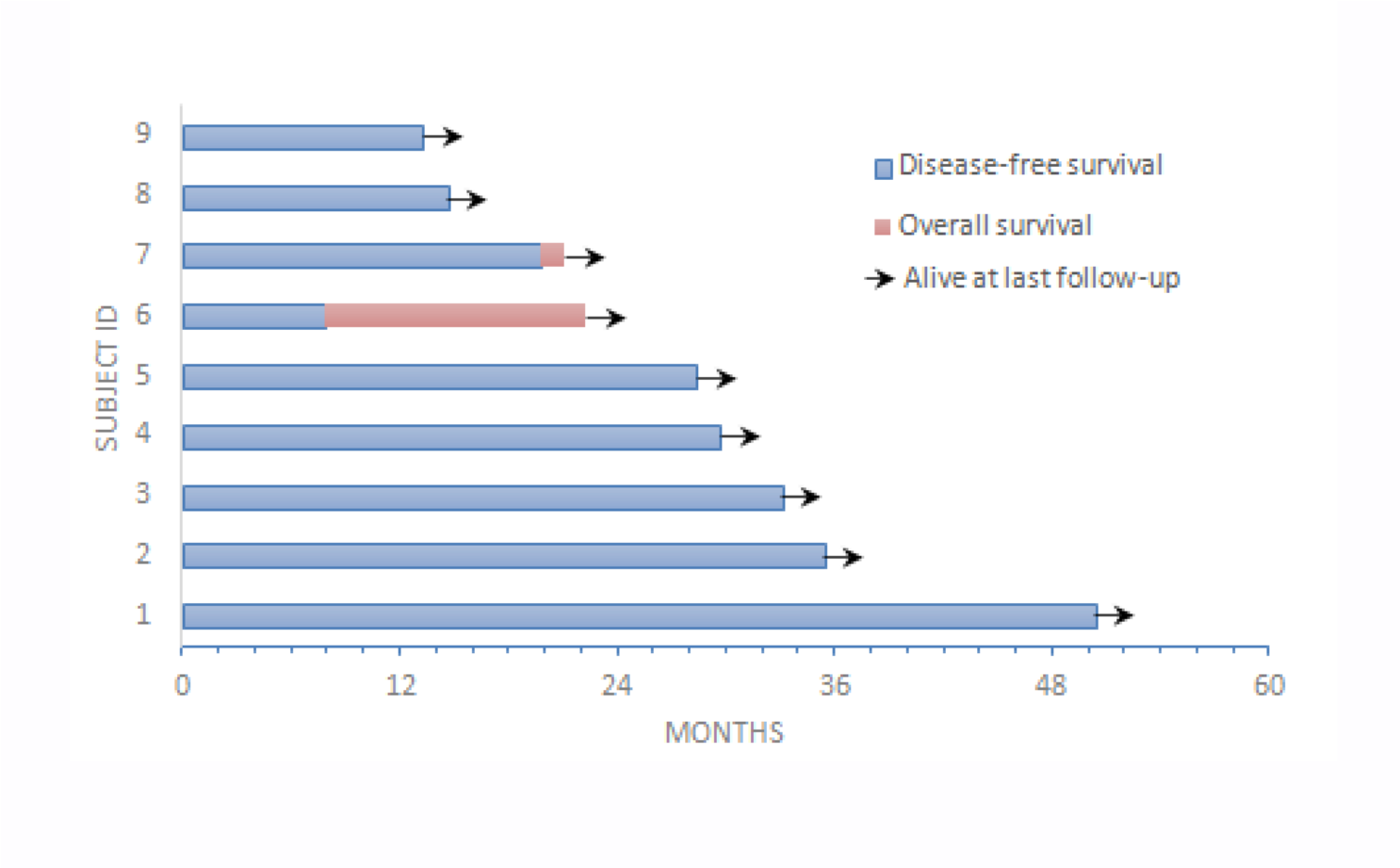

Figure 4

A swimmer survival plot. Each bar represents one subject in the study. The right arrows indicate continued survival since the most recent follow-up.