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

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Research
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 by surgery has become the standard of care for potentially resectable superior sulcus (SS) tumours, owing to the promising results of two prospective multi-institutional randomised phase II trials (Southwest Oncology Group 9416 [2007][1] and Japan Clinical Oncology Group 9806[2008][2]). The five-year overall survival (OS) of patients treated in this manner was reported to be 40–60%.[1–3] and compared to induction radiotherapy alone, neoadjuvant CCRT decreased the incidence of local relapse from 40–12%.[1] In order to decrease local failure rates and ultimately improve OS, intraoperative radiotherapy (IORT) was explored as a treatment for SS tumours. IORT has been primarily performed via brachytherapy, which delivers a highly localised dose of radiation to tumours while sparing adjacent normal tissue. In brachytherapy, radioactive seeds are permanently implanted into tumours with the help of image guidance. Moreover, studies have reported that brachytherapy achieves high local control in selected patients with SS tumours.[4–6] However, intraoperative brachytherapy combined with perioperative radiotherapy has had no influence on OS or regional control when complete resection is achieved, as noted in the Ginsberg et al study,[6] the largest retrospective IORT study to date, which included 102 patients treated with brachytherapy. The value of intraoperative brachytherapy in patients with complete resection remains in question. Therefore, a novel therapy is required to increase
the local control of SS tumours. The purpose of this pilot study was to assess the feasibility and safety of IORT with low-energy X-rays for the treatment of SS tumours.

Methods

Study Design

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

Patient Eligibility

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

Treatment

A flow-chart of patient care and the numbers of patients treated at each time point in the study is shown in Fig. 1. All patients were evaluated during a lung cancer multidisciplinary team (MDT) meeting to discuss their treatment. The decision to administer neoadjuvant treatment depended on the evaluation of resectability and the patient's choice. If the tumour was technically resectable, surgery was performed without neoadjuvant treatment. The neoadjuvant chemotherapy regimen for patients with potentially resectable tumour was two cycles of platinum-based doublet regimen, consisting of cisplatin (50 mg/m² d1, 8) and etoposide (50 mg/m² d1-5) for concurrent chemotherapy, and docetaxel (120 mg/m² d1) and cisplatin (50 mg/m² d1) for induction chemotherapy. Radiotherapy, with a dose of 50 Gy/25 fractions/5 weeks, was performed via intensity-modulated radiation therapy (IMRT) with an energy of 6 MV. Patient evaluations were performed after four weeks of neoadjuvant treatment via positron emission tomography-computed tomography (PET-CT) or computed tomography (CT). Video-assisted thoracoscopic surgery (VATS) lobectomy with systematic mediastinal lymphadenectomy was performed for all patients.

IORT was administered to the tumour bed via the PRS400 Photon Radiosurgery System (Carl Zeiss, Germany), also called the Intrabeam system, when surgical margin status was defined by the surgeon as
close margins, as these can cause a high risk of relapse. The Intrabeam system is a miniature, high-dose rate and low energy X-ray (50 kV) source which emits photon radiation directly to a tumour or tumour bed. The dose rate at the surface of applicators is related to the size of the applicator. A set of rigid reusable spherical applicators is available with diameters ranging from 1.5 to 5.0 cm. The maximum length of tumour bed was measured after resection by the surgeon. The tumour bed on the chest wall was delineated on preoperative CT scans by a radiation oncologist and regarded as a curved surface, thus the diameter of applicator was calculated by the formula: diameter = 360 • arclength ÷ [π • central angle (degrees)] (Fig. 2). A radiation dose was specified at the reference point at a distance of 0.5-1.0 cm from the applicator surface, which was determined based on the distance to adjacent critical organs. The applicator was positioned in direct contact with the target tissue. Figure 3 illustrates an anatomical diagram of the Intrabeam system technique in patients with SS tumour. Equivalent dose in 2-Gy fractions (EQD2) was calculated for the EBRT and IORT course according to the linear-quadratic model, using an α/β value of 2 Gy for spinal cord and brachial plexus. The maximum point dose to the spinal cord or brachial plexus was limited to 50 Gy²/².

After IORT, surgical clips were placed in the radiation field to mark the IORT area on CT scans. Postoperative CT was then performed after extubation. The postoperative CT images were transferred to Eclipse TPS and subsequently fused with the corresponding preoperative CT images, in order to calculate and evaluate dose distribution and the radiation dose of organs at risk (OAR).

Follow-up

Follow-up monitoring was implemented at 4 and 12 weeks after surgery, then every three months during the first two years, and every 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 after treatment. Both a thoracic surgeon and radiation oncologist assessed acute and late toxicity in accordance with version 4.0 of the National Cancer Institute's Common Toxicity Criteria for Adverse Events (NCI-CTCAE 4.0) at the date of each follow-up visit.

For our literature review, we performed an extensive search of both the PubMed and Medline databases in December 2018 using the following search terms: “superior sulcus tumour”, “apical lung cancer”, and “intraoperative radiotherapy”.

Results

A total of nine treatment-naive patients (seven males and two females) with clinical stage II-III SS tumours were enrolled in this pilot study between August 22, 2014 and November 30, 2017. The patients’ clinical features and treatment details are presented in Table 1. Two of the nine patients were evaluated to be resectable at baseline by the MDT, and received surgery without neoadjuvant treatment. One of the other seven patients refused radiotherapy and received neoadjuvant chemotherapy alone. Of these nine patients, six underwent lobectomy, chest wall resection and systemic lymph node dissection via VATS, and three underwent lobectomy and systemic lymph node dissection. Of these three, two underwent lobectomy
because their tumours greatly regressed after neoadjuvant treatment, as indicated by the fluorodeoxyglucose F18 uptake seen on their post-neoadjuvant treatment PET-CT images, and the fact that no tumour cells were found during intraoperative frozen section analysis. In the third patient, chest wall invasion was suspected on preoperative images, and during surgery, we saw that the patient's tumour actually infiltrated the parietal pleura without rib invasion. We were able to completely excise and the resection margin was negative on intraoperative frozen section diagnosis. Therefore, chest wall resection was no longer considered necessary in these three cases. Postoperative histopathology confirmed complete (R0) resection in all patients. A radiation dose of 6.5-8.0 Gy at a distance of 0.5-1 cm from the applicator's surface was delivered to all patients during surgery.

Anaemia was the most common acute complication observed, with grade 3 anaemia (Haemoglobin < 8.0 g/dL) occurring in three patients who underwent preoperative CCRT. Additionally, one patient developed a fever of over 39°C at six hours post-surgery, indicating pulmonary infection. After this patient underwent four days of antibiotic therapy, the patient's body temperature dropped back to normal. Another patient had a prolonged air leak after the operation, which was successfully treated on the 12th postoperative day. This patient was discharged three days after his postoperative thoracic CT scan revealed leakage resolution. One patient had grade 1 brachial plexus injury with right shoulder numbness. Radiation myelopathy, wound dehiscence or infection, pulmonary and bronchopleural fistulae, empyema, cardiac failure, and respiratory failure were not observed during the study period. Each patient's 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 average follow-up period of 29.4 months (range, 13.3–50.4 months). The median disease-free survival period was 28.3 months. During the follow-up period, distant metastasis was observed in two patients. Of these two patients, one suffered from single contralateral lung metastasis at 11 months post-surgery, so this patient received radiofrequency ablation. The other had multiple mediastinal lymph node and pericardial metastasis, so this patient received chemotherapy. Figure 4 shows the survivorship plot of patients in our study.

Discussion

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

In our study, IORT with low-energy X-rays was performed successfully and safely in all nine SS tumour patients. No in-field recurrence was observed, and the longest follow-up period was over four years. Moreover, it achieved high local control in patients with a high risk of local relapse. Severe anaemia (≥
Grade 3), the most common acute toxicity-related complication seen in our study, was observed in patients who received preoperative CCRT. This may have been due to the inability of the patients’ hematopoietic systems to recover from induction CCRT. The other side effects observed in our study were mild. Notably, in a study by Martinez-Monge et al.,[5] 17/18 patients with SS tumours were treated with preoperative CCRT followed 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, two of their patients died as a result of complications, and their treatment-related morbidity was high. Additionally, the postoperative lengths of hospital stay in our study were a little longer than those in a previously published report,[7] as we had patients scheduled to undergo CT after extubation, which took three to four postoperative days. Furthermore, the chest wall was conserved in three patients due to the tumour-free margins observed during the intraoperative frozen section analysis and IORT applied to tumour beds in our study.

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

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

**Conclusions**

Our research has significant clinical applicability, as this report presents the first patients to receive low-energy X-ray intraoperative radiation for the treatment of SS tumours. Moreover, our results also suggest that this method can achieve high local control. IORT with the Intrabeam system is a technically feasible and relatively safe treatment modality for patients with superior pulmonary 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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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 | Left shoulder | Right shoulder | Right shoulder | No symptom | Cough for 1 month | Cough and hemoptysis | Left shoulder | No symptom |
| | 10 kg for 1 month | pain for 1 month | pain for 1 month | pain for 1 week | for 1 month | pain for 2 years | |
| 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 | None | 30 | 80 | 60 | None | 60 | None | None | None |
| (Pack/year) | | | | | | | | | |
| Pre-treatment | Chemo | CCRT | CCRT | - | CCRT | CCRT | CCRT | CCRT | CCRT |
| Tumour response | PR (-30%) | PR (-30%) | PR (-40%) | - | PR (-43%) | CR | SD (-20%) | SD (-26%) | |
| Surgery | Lobectomy + rib 2nd | Lobectomy + rib 2nd + 3rd | Lobectomy + rib 3rd + 4th | Lobectomy + rib 1st + 2nd | Lobectomy + rib 2nd | Lobectomy + rib 3rd | Lobectomy + rib 2nd | Lobectomy + rib 2nd | Lobectomy + rib 3rd |
| 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     | 8.0 Gy (0.5 cm) | 6.5 Gy (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   |
| Radiation time (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   | Brachytherapy         | EBRT            | 5 y OS: 26% (all); IORT+R0 resection: NS; IORT+R1, R2 resection: 9% |
| Martinez-Monge et al. (1994)  | 18  | IOERT                 | C+CCRT+S+IORT(15) | m follow-up: 24+ m                          |
|                               |     | 6-18 Mev              | CCRT+S+IORT (2)  | 4 y OS: 56.2%                               |
|                               |     | 10-15 Gy              | CCRT (1)        | 4 y LC: 91%                                 |
| Ohta et al. (2001)            | 2   | Brachytherapy         | C+S+IORT (1)    | Follow-up: 6 m and 10 m                      |
|                               |     | 192 Ir (21 Gy and 30 Gy) | S+IORT (1)     | No recurrence                               |
| Van Geel et al. (2003)        | 26  | Brachytherapy         | EBRT (3)        | median follow-up: 18 m                      |
|                               |     | 192 Ir (10 Gy)        | EBRT+S (2)      | median OS: 14 m                             |
|                               |     |                      | EBRT+S+IORT (21) | LC: 85%                                      |
| Torre et al. (2009)           | 24  | Brachytherapy         | C+S (18)        | 5 y OS: 56.6%                               |
|                               |     | 192 Ir (10 Gy)        | CCRT+S (15)     | IORT: NS                                    |
|                               |     |                      | IORT (7)        |                                              |

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.