Proton Beam Therapy for Inoperable Recurrence of Bronchial High-grade Mucoepidermoid Carcinoma

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Received November 3, 2011; accepted March 7, 2012

We report the case of a 17-year-old patient who received four courses of proton beam therapy for inoperable recurrent high-grade bronchial mucoepidermoid carcinoma of the chest wall and lymph nodes. The equivalent doses in conventional fractionation of 79.2–80.6 Gy were applied to the tumor from the first to third courses of proton beam therapy; the hemi-chest wall was also irradiated prophylactically in the third course. The irradiated tumor recurred marginally and liver metastasis developed, but tumor size within the irradiated field was suppressed. Proton beam therapy was also applied to the marginally recurrent tumor in the fourth course. The patient died of cancer about 5 years after the first course of proton beam therapy—about 9 years after the initial diagnosis and surgery. Repeated irradiation of the mediastinum and chest wall with photon radiotherapy is often limited by side-effects in the heart, esophagus and spinal cord. However, no severe late complications in critical organs were detected in this case. Only a Grade 2 skin reaction and lymphatic edema were observed. Therefore, high-dose proton beam therapy may be an option as a salvage therapy with less toxicity to normal tissues compared with photon radiotherapy and provide an alternative to repeated surgery.

Key words: proton beam therapy – high-grade mucoepidermoid carcinoma – bronchial carcinoma – inoperable case – pediatrics

INTRODUCTION

Bronchial mucoepidermoid carcinoma (MEC) is a rare disease that accounts for about 10% of primary lung neoplasms in childhood and adolescence (1,2). MEC is more likely to show local invasion than metastatic disease, the latter being relatively rare (3). Surgical resection is the main treatment for MEC, whereas radiotherapy and chemotherapy are not well established for this disease. High-dose radiotherapy was reported to be required in a case of MEC in the salivary gland (4). It is often difficult to perform repeated radiotherapy because of overlapping of irradiation fields. In this context, proton beam therapy (PBT) is advantageous since it has excellent dose localization because of a Bragg peak, in which the dose falls off rapidly at the end of the beam range at a depth within the patient (5). Herein, we report a case of a 17-year-old girl with inoperable recurrent bronchial MEC who was treated with four courses of PBT.

CASE PRESENTATION

HISTORY

The patient was a girl diagnosed with primary bronchial carcinoma of Stage T3N0M0 when she was 13 years old (6).
She underwent pneumonectomy; the pathologic findings showed MEC with high-grade histology. Over a period of about 4 years after pneumonectomy, she underwent three surgical resections because of repeated mediastinal lymph node recurrences (Fig. 1). After the third resection, a gross residual lymph node remained. She was referred to our hospital for PBT for the remnant disease when she was 17 years old. Repeated PBT was performed four times for persistent inoperable recurrence over about 3 years until the patient’s death.

**Proton Beam Therapy**

The photon equivalent dose [gray equivalent dose, Gy(RBE)] was defined as the physical dose (Gy) × the relative biological effectiveness (RBE) of the proton beam, assigned a value of 1.1 (7). The equivalent dose in conventional fractionation (2.0 Gy per fraction: EQD2) was calculated based on a linear quadratic model, assuming $\alpha/\beta = 10$ for the tumor.

The treatment target volume was defined as the recurrences, which were identified by computed tomography and/or positron emission tomography (PET) with $^{18}$F-fluorodeoxyglucose, plus margins of 0.5–1 cm.

The first course of PBT was performed with a total dose of 66 Gy(RBE) in 15 fractions (EQD2: 79.2 Gy) delivered to the gross residual mediastinal lymph node lesion after surgery (Fig. 2a) via two posterior ports. Seven months after this treatment, the second PBT was directed to the paratracheal lymph node metastases, which were located above the first irradiated field (Fig. 2b). A dose of 72.6 Gy(RBE) in 22 fractions (EQD2: 80.5 Gy) was delivered via two anterior ports. Prophylactic lymph node irradiation was not considered in the first and second treatments. The third course, consisting of 78.1 Gy(RBE) in 33 fractions (EQD2: 80.6 Gy), was delivered to the recurrent lesion in the left chest wall and invading the ribs, which appeared inferior to the past irradiated fields (Fig. 3). This time, the hemi-chest wall was also irradiated prophylactically with a dose of 50.6 Gy(RBE) in 23 fractions (EQD2: 51.4 Gy). Because the chest wall was curved and larger than one port size of the proton beam, the patch-field technique was used (8,9); the target was divided into two segments and a treatment field was determined for each target. The treatment field and dose distribution were optimized to minimize high- and low-dose areas at the junction of the fields. No tumor was detected by PET after each treatment. A disease-free status was maintained for 1 year after the third course of PBT. However, the tumor repeatedly recurred in the paratracheal, left infraclavicular lymph nodes, the left chest wall and the liver. Except for the liver metastases, these were considered to be marginal recurrences. A fourth course of PBT for the paratracheal lymph nodes, the
infraclavicular lymph nodes and the chest wall lesion was performed with doses of 59.4 Gy(RBE) in 30 fractions (EQD2: 59.3 Gy), 66 Gy(RBE) in 30 fractions (EQD2: 67.1 Gy) and 55.4 Gy(RBE) in 28 fractions (EQD2: 55.3 Gy), respectively (Fig. 4). Though we selected different port angles from previous irradiation ports, the field for the chest wall recurrence lesion overlapped with the irradiated fields from the third course, and the doses were increased to 106–133.5 Gy(RBE) in a small portion of soft tissue. There was no overlap on the mediastinum, heart, esophagus or spinal cord.

Chemotherapy was performed after the fourth course of PBT. The irradiated tumors disappeared over 1 year, but liver and mediastinal lymph node metastases progressed outside of the irradiated field. The patient died of MEC 5 years after her first visit to our hospital, which was about 9 years after the initial diagnosis.

Toxicities were limited to a Grade 2 skin reaction and left arm lymphatic edema, which were observed at 4 years after the first irradiation (10). No severe late complications of critical organs such as the heart, esophagus and spinal cord were detected.

DISCUSSION

Primary pulmonary malignancy is rare in children. MEC accounts for approximately 10% of these malignancies (1,2) and is classified pathologically into low, intermediate and high grade in the Brandwein grading system (11). More than 95% of the cases of MEC are low or intermediate grade in children and these cases frequently have a good long-term prognosis. However, high-grade MEC is not an indolent disease (12). Yousem and Hochholzer reported that among 13 patients with high-grade MEC, four patients had recurrence and died of their disease (13). However, even high-grade MEC has only minimal metastatic potential, but often shows locally aggressive invasion (12,14). Therefore, radical local treatment, mainly through surgical resection, provides patients with the best chance of long-term survival. In contrast, the role of radiotherapy for bronchial MEC has not been widely discussed because the incidence of regional involvement of MEC is low. In a case of primary MEC of the salivary gland, Chen et al. (4) recommended a dose in excess of 66 Gy, and the low radiosensitivity of MEC indicates that high-dose irradiation is required to obtain good local control (14).

Compared with photon radiotherapy, PBT permits administration of a high dose of radiation to a limited volume of the tumor while delivering very low doses to non-cancerous
neighboring tissue via a small number of ports (15,16). Using a photon beam, repeated radiotherapy for the mediastinum and extended chest wall is limited by toxicity in the heart, esophagus and spinal cord, especially for a growing patient. However, we can spare these neighboring critical organs using proton beams despite using four times irradiation. Recently, intensity-modulated radiotherapy or stereotactic body radiotherapy has been used to improve dose distribution and treatment effect. However, because these techniques need more ports to create an optimal dose distribution than does PBT, they are associated with a much larger low-dose irradiated area. Therefore, we believe that PBT has a great advantage during repeated therapy in terms of minimizing overlapping area. In fact, our patient had no severe late toxicities of critical organs, despite receiving high doses of irradiation during repeated PBT and showing a rapid response to therapy. Side-effects were limited to a Grade 2 skin reaction and lymphatic edema. Also, the survival time of our patient—9 years after the first diagnosis—is comparable to other reports of 5-year survival rates of 25–31% in patients with high-grade MEC (17,18).

Considering that PBT was used repeatedly for persistent inoperable recurrence in our case and resulted in little toxicity in normal tissues, we believe that PBT offers an option as a salvage therapy and an alternative to repeated surgery.

Conflict of interest statement
None declared.

References