Eur Spine J (2014) 23 (Suppl 2):S222–S227
DOI 10.1007/s00586-013-3056-2

CASE REPORT

Reconstruction using a frozen tumor-bearing vertebra in total en bloc spondylectomy can enhance antitumor immunity

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Received: 1 April 2013 / Revised: 25 September 2013 / Accepted: 25 September 2013 / Published online: 5 October 2013

Abstract
Purpose Distant metastases from thyroid carcinoma are successfully cured if they take up radioiodine (^{131}I), are of small size, and located in the lungs. Bone metastases have the worst prognosis because ^{131}I therapy and external beam radiotherapy are less effective. Our propose here is to report a patient with solitary spinal metastasis and multiple lung metastases from thyroid carcinoma, whose spinal metastasis was treated by total en bloc spondylectomy (TES) enhancing antitumor immunity using frozen tumor-bearing bone for spinal reconstruction.
Methods The patient was a 37-year-old male who had solitary spinal metastasis at T4 and multiple lung metastases from thyroid carcinoma. ^{131}I therapy for the multiple lung metastases resulted in no effect because the apparent ^{131}I uptake was observed only in T4 metastasis. We performed a TES of T4 with cryotreatment. After en bloc excision of T4, the excised tumor-bearing vertebra was frozen by liquid nitrogen. In spinal reconstruction, the frozen vertebra was used in a mesh cage inserted into the anterior defect.
Results After surgery, the thyroglobulin level decreased without any other adjuvant therapy and the serum levels of INF-γ and IL-12 increased. This indicates antitumor immunity was activated. Then, ^{131}I therapy became effective to the lung metastases causing the tumors to decrease in size and number. Three years after surgery, progression in the lung metastases, other metastasis, and local recurrence have not been observed.
Conclusions TES with cryotreatment as presented is a novel surgery which can enhance antitumor immunity against other visible or non-visible metastases.

Keywords Antitumor immunity · Total en bloc spondylectomy · Liquid nitrogen · Reconstruction

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Introduction

Cancer is one of the leading causes of death in developed countries. However, recent data suggest a progressively improving trend in survival of patients with cancer. The skeleton is the third most common site of metastases after the lungs and liver, with the spinal column most frequently involved [1]. Symptomatic spinal metastases will become more prevalent as the rates of survival improve for many common cancers. Several therapeutic options for spinal metastases exist with the goal of eliminating pain, local disease progression, spinal instability, and reversing or preventing neurological compromise [2, 3]. Total en bloc spondylectomy (TES) is a surgical procedure designed to achieve complete resection en bloc of an aggressive benign spinal tumor or a malignant spinal tumor, and provide an adequate tumor margin. Using this procedure can result in a decrease in the rate of local recurrence plus longer survival [4, 5].

Cryosurgery is recognized as a highly efficient, minimally invasive method of treating malignant neoplasms. There has also been significant interest in another aspect of freezing tumors and leaving them in situ for the body to absorb, the ability to stimulate an immunologic response to tumor-specific antigens in the frozen tissue [6]. Tsuchiya et al. [7] reported reconstruction using frozen tumor-bearing autograft treated by liquid nitrogen for malignant

tumors of extremities and pelvis. The results have proved that the reconstruction is a safe and effective method. We applied this technique to TES surgery.

Here we present a patient with solitary spinal metastasis and multiple lung metastases from thyroid carcinoma, whose spinal metastasis was successfully treated by TES enhancing antitumor immunity using frozen tumor-bearing vertebra for spinal reconstruction. This surgery was approved by the ethics committee of Kanazawa University, and written consent was obtained for the publication of this case.

Case report

A 37-year-old man had tumor excision for pT3N1aM0 thyroid carcinoma, papillary type. He had total thyroidectomy for tumor recurrence 4 years after the initial surgery. At that time, multiple lung metastases and solitary spinal metastasis at T4 were detected. After the second surgery, the administration of radioiodine (^{131}I) was provided for the multiple lung metastases. However, that was not effective because the apparent ^{131}I uptake was observed only in T4 metastasis. He was referred to our hospital for the purpose of radical surgery for T4 metastasis four and a half years after the initial surgery.

On presentation at admission to our hospital, he had back pain but did not have any neurologic symptoms. Computer tomography (CT) showed multiple (more than 20) lung metastases which had not abated after the radioiodine therapy. Magnetic resonance imaging (MRI) showed T4 spinal metastasis with vertebral body involvement (Fig. 1) and further examinations did not reveal other distant metastases. Tomita score of this case was 6 points [5]. We planned a novel surgery which consisted of TES of T4 and cryotreatment using the resected vertebra bearing tumor in spinal reconstruction (Fig. 2).

Operative technique

The patient was placed in the prone position on the operating table. En bloc resection of the posterior element of T4 was performed by pediculotomy using a flexible multifilament thread wire saw [8] (T-saw; Promedical Co, LTD, Kanazawa, Japan). T4 nerve roots were ligated and cut bilaterally. The anterolateral aspect of the vertebral body was dissected, with care taken not to violate the tumor margin. After posterior instrumentation had been applied, the T3/4 and T4/5 discs were cut off using chisels. T4 vertebral body was removed en bloc posteriorly. After removal of surrounding musculoligamentous tissues, the excised tumor-bearing vertebra was frozen by placing it in liquid nitrogen for 20 min. In spinal reconstruction, the frozen vertebra was crushed into pieces and packed into a titanium mesh cage. The cage was then inserted into the anterior defect. The posterior instrumentation was adjusted to slightly compress the inserted cage. The operating time

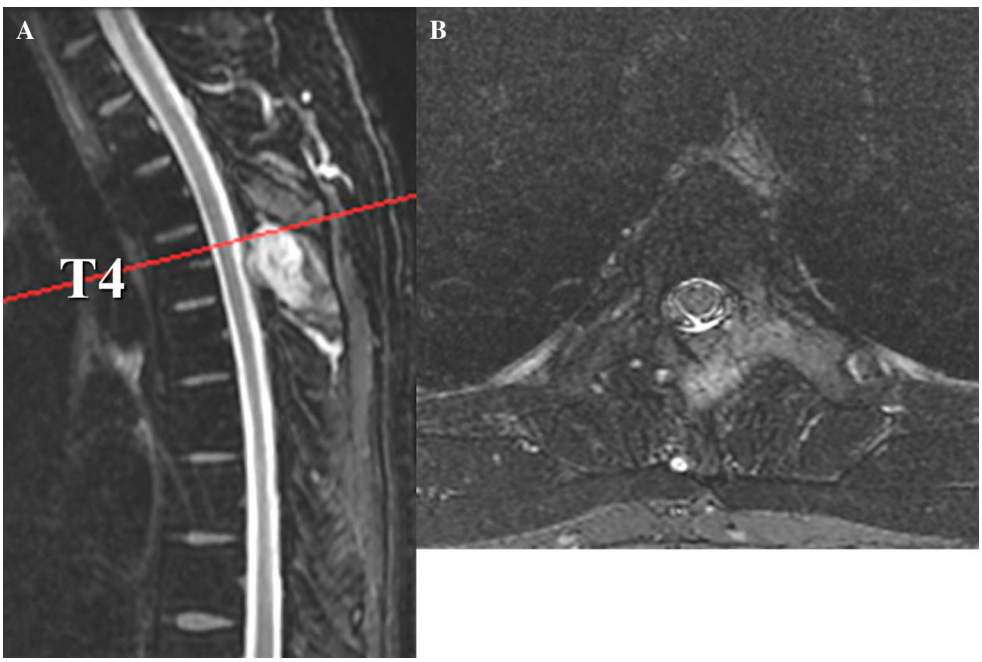

Fig. 1 Preoperative T2-weighed MRI showing T4 metastasis. **a** Sagittal view, **b** axial view. The tumor invaded into the vertebral body through left pedicle

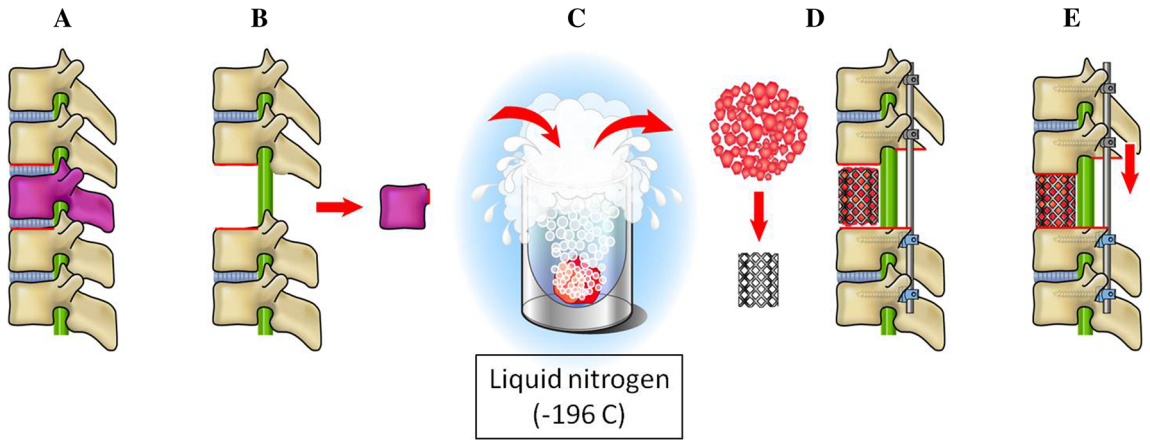

Fig. 2 Schematic diagrams of TES with cryotreatment. **a** Metastatic tumor involving the spine, **b** en bloc resection of the whole affected vertebra, **c** the vertebra was put into liquid nitrogen and the frozen vertebra was crushed in pieces and packed into a titanium mesh cage, **d** the cage was inserted into the anterior defect, **e** spinal shortening was applied to stabilize the cage

was 351 min. The intraoperative blood loss was 860 ml. The operative procedure of TES has been described in detail elsewhere [9].

Postoperative course

After the surgery, his back pain was no longer present. He did not have any postoperative complications such as surgical site infection. We checked serum thyroglobulin (Tg) values as tumor marker of thyroid cancer. The preoperative Tg level was 768 ng/ml. That value remarkably decreased to 171 ng/ml two months after surgery. This decrease was caused by tumor excision of T4. Then, Tg decreased further to 114 ng/ml five months after surgery without any other adjuvant therapy. Tg has a half-life of around 2–4 days.

We analyzed blood samples from the patient before surgery and three months after surgery to measure the levels of interferon-γ (IFN-γ, human, ELISA Kit; Quantikine R and D Systems, Minneapolis, MN, USA) and interleukin-12 (IL-12, human, ELISA Kit; Quantikine R and D Systems) cytokines suggestive of antitumor immunity. The preoperative IFN-γ level was 40.4 IU/ml; this increased to 48.6 IU/ml three months after surgery. Similarly the preoperative level of IL-12 was 29.7 pg/ml; this increased to 137.0 pg/ml three months after surgery.

When the administration of radioiodine was provided for the multiple lung metastases six months after surgery, the apparent ^{131}I uptake was observed in the lung metastases. After the radioiodine treatment, the lung metastases showed decreases in their size and number and the Tg level decreased to 71 ng/ml; this value is within the normal range (Fig. 3). He has undergone another three courses of radioiodine therapies additionally. Three years after the TES combined with cryotreatment of T4, he is still alive without any symptoms. There have not been any problems, such as instrument failure or pseudoarthrosis, in the reconstructed spine (Fig. 4). The Tg level is 55–70 ng/ml, which is still within the normal range. Progression in the lung metastases has not been observed and there has been no other metastasis or local recurrence.

Discussion

Thyroid cancer is the most common endocrine malignancy, although representing fewer than 1 % of all human tumors. Differentiated thyroid carcinoma includes the papillary and follicular histotypes and their variants, accounting for more than 90 % of all thyroid cancers [10]. Both papillary- and follicular-differentiated thyroid cancers have usually a good prognosis, with an overall mortality of less than 10 % [11]. Distant metastases are more successfully cured if they take up ^{131}I, are of small size, and located in the lungs (not visible on radiographs). Lung macronodules may benefit from ^{131}I therapy, but the definitive cure rate is very low [12, 13]. Bone metastases have the worst prognosis even when aggressively treated by a combination of ^{131}I therapy and external beam radiotherapy, because these treatments are less effective for bone metastases [14, 15]. TES as presented here afforded two benefits: (1) radical resection of spinal metastasis; (2) elevation of effectiveness of radioiodine therapy for lung metastases. The lung metastases in this patient had little ^{131}I uptake before surgery because of the concentration of ^{131}I uptake to the spinal metastasis at T4. This resulted in lessening the effect of radioiodine therapy to the lung metastases. After the TES of T4, the therapy became effective to the lung metastases causing the tumors to decrease in size and number.

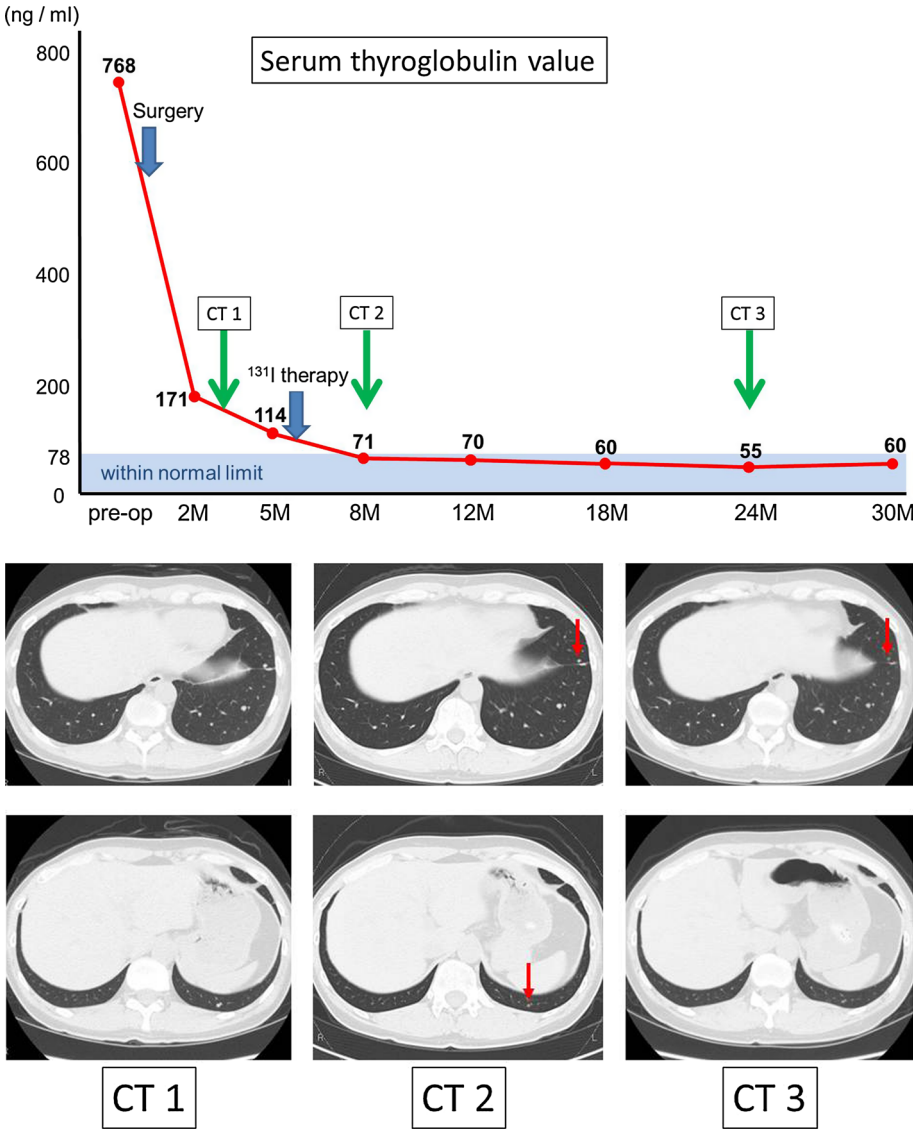

Fig. 3 Clinical course of the patient undergoing TES with cryotreatment for spinal metastasis. CT showed the decreases of the lung metastases in their size and number. (See *arrows* (CT 1) before surgery (CT 2) 3 months after surgery (CT 3) 8 months after surgery

The other additional benefit of TES as presented here is antitumor immune response by cryotreatment. Cryotreatment of a bone tumor using a specimen frozen using liquid nitrogen is a type of cryosurgery, and previous reports have suggested immune system activation brought about by cryosurgery. Ablin et al. [16] described several patients in whom spontaneous regression of metastases occurred after cryosurgery of a primary prostate cancer. In animal models, cryosurgery of tumor tissue resulted in rejection of a tumor re-challenge [6] and inhibition of secondary and metastatic tumor growth [17]. TNF-α, TNF-γ and IL-12 levels have shown increases in several cryosurgery models [6, 16, 17]. Increases in cytotoxic activity and natural killer T cell activity have been measured in lymphocytes from lymph nodes or spleens that are recipient sites of tumor drainage [6]. These reports indicate that cryosurgery not only destroyed the tumor tissue directly by freezing and thawing but also induced a specific antitumor effect by an immune mechanism via dendritic cells that was stimulated by tumor antigens released by cryonecrotic tissue [18]. Nishida et al. [19] reported that re-implantation of tumor tissue frozen using liquid nitrogen induces antitumor activity against murine osteosarcoma and the serum levels of INF-γ and IL-12 increased after treatment [20]. Moreover, they reported on a patient with metastases from renal cell carcinoma involving the lungs and bone. The lung metastases disappeared after reconstruction using the resected specimen treated by liquid nitrogen for the bone metastasis in conjunction with cytokine immunotherapy [21]. This antitumor effect enhanced the systemic immune reaction and reduced tumor growth and metastases. In our patient, we observed a decrease in the serum level of Tg along with increases of the serum INF-γ and IL-12 without any other adjuvant therapy after TES using frozen autograft

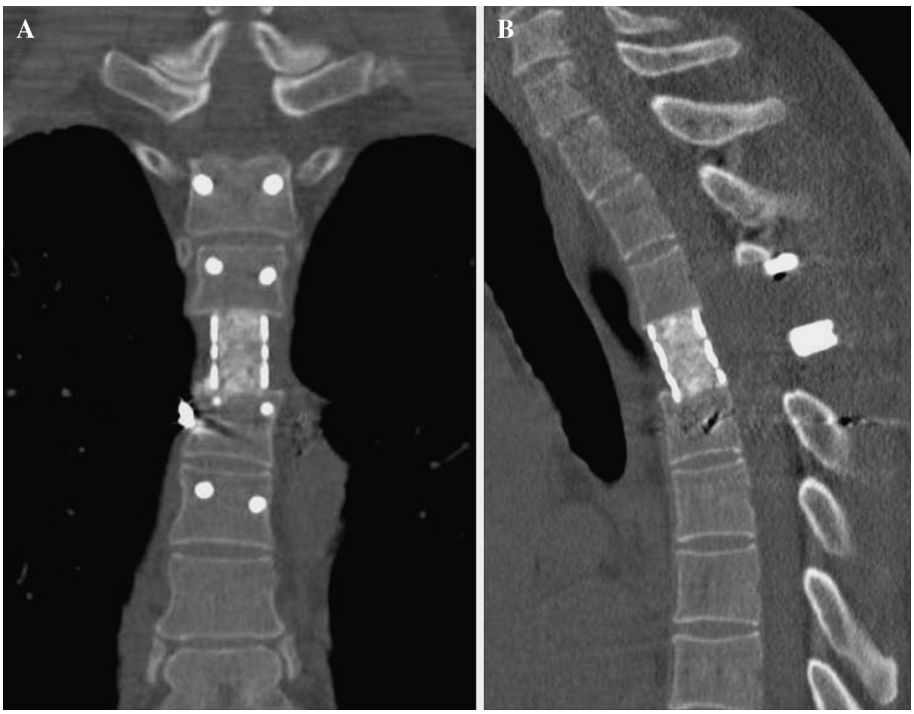

Fig. 4 Postoperative CT after TES of T4. **a** Sagittal view, **b** coronal view

inside a cage. This suggests that the tumor antigens released by the frozen tumor-bearing vertebra induced an antitumor immunological activation definitely.

Although we have still to collect clinical data from other patients treated using this therapy, TES with cryotreatment as presented is a novel surgery which provides oncological complete tumor resection of spinal metastasis as well as possibility of antitumor immune enhancement against other visible or non-visible metastases.

Acknowledgments The authors thank William C. Hutton DSc, for their kind criticism and advice.

Conflict of interest None of the authors has any potential conflict of interest.

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