

Title:

Late recurrence of non-seminomatous germ cell tumor successfully treated with intensity-modulated radiation therapy

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Running title

NSGCT successfully treated with IMRT

## Abstract

We report on a 41 year-old man with late recurrence of non-seminomatous germ cell tumor (NSGCT), which was successfully treated with intensity-modulated radiation therapy (IMRT). For the residual retrocrural tumor invading 11<sup>th</sup> and 12<sup>th</sup> thoracic vertebra with an abnormal level of tumor marker ( $\alpha$ -fetoprotein: 23.2 ng/ml) after salvage chemotherapy, chemotherapy could not be continued due to its neurotoxicity and surgery could not be performed due to the location. In this situation, IMRT achieved complete response of tumor marker. He remains in complete clinical remission after 3 years. The efficacy of radiotherapy, especially IMRT, for NSGCT is discussed.

## Mini-abstract

We report on a 41 year-old man with late recurrence of non-seminomatous germ cell tumor, which was successfully treated with intensity-modulated radiation therapy.

## Key words

non-seminomatous germ cell tumor, intensity-modulated radiation therapy, late recurrence

## Introduction

The prognosis for non-seminomatous germ cell tumor (NSGCT) of the testis has been dramatically improved with a treatment protocol of cisplatin-based chemotherapy followed by surgical resection of residual tumor [1]. However, a small proportion of patients subsequently suffered relapses, and patients with recurrence more than 2 years since initial chemotherapy have been reported to have significantly poor response to salvage surgery or chemotherapy [2]. Although surgical treatment for remaining tumor after salvage chemotherapy can achieve prolonged survival [3], the tumors are occasionally unresectable. Meanwhile, although radiation therapy for NSGCT had been considered to have little effect for NSGCT [4], the irradiation technology has progressed dramatically for recent years. We herein report a case with late recurrence of NSGCT treated with an advanced irradiation method of intensity-modulated radiation therapy (IMRT).

## Case report

A 25 year-old patient underwent right inguinal orchitectomy for a testicular tumor in October 1991. A mixed germ cell tumor, containing components of embryonal carcinoma, yolk sac tumor and teratoma, was diagnosed. The serum levels of tumor markers were

elevated prior to orchitectomy with 10254 ng/ml  $\alpha$ -fetoprotein (AFP) and 376 mIU/ml human  $\beta$ -chorionic gonadotropin ( $\beta$ -HCG). Computerized tomography (CT) showed a huge retroperitoneal lymph node metastasis. Three cycles of chemotherapy containing cisplatin, cyclophosphamide, vinblastine, actinomycin D and bleomycin and following retroperitoneal lymph node dissection was performed. Pathological diagnosis for resected tumor was teratoma. He had regular follow-up with no evidence of tumor for the first 10 years, but had been lost to follow-up for the next 5 years. In September 2007, at the age of 41, he visited our clinic with a complaint of flank pain. CT findings showed a solitary 9 cm retrocrural mass invading 11<sup>th</sup> and 12<sup>th</sup> thoracic vertebrae and surrounding the thoracic aorta. The serum levels of AFP and  $\beta$ -HCG were 2057 ng/ml and 5.2 mIU/ml, respectively. He received salvage chemotherapy with diagnosis of a late recurrence of non-seminomatous germ cell tumor. After one cycle of cisplatin and etoposide and two cycles of cisplatin and paclitaxel and ifosfamide, he suffered from severe chemotherapy-induced peripheral neuropathy which had been sustained at the level of grade 2. Additional two cycles of chemotherapy with alternative regimens containing irinotecan and nedaplatin worsened neuropathy to grade 3, indicating difficulty for further chemotherapy. At this point, AFP still showed an elevated level (23.2 ng/ml) and AFP-L3 fraction was also high (63.6%) although  $\beta$ -HCG returned to the

normal value. Moreover, the residual retroperitoneal mass in positron emission tomography (PET) showed uptake of 18 F-deoxyglucose (FDG) (Fig.1). Although these data suggested viable tumor cells remaining, we judged curative surgery with the resection for the invaded vertebral body and aorta to be highly challenging and difficult to perform because of a high risk of severe paraplegia and lethal bleeding.

We selected radiation therapy with a simultaneous integrated boost IMRT (SIB-IMRT) technique (Fig.2) to deliver enough doses to all targets including vertebral lesions while sparing the spinal cord and kidneys. The clinical target volume (CTV) definition was based on the PET/CT and MRI. The planning target volume (PTV) was created by adding an automatic isotropic 5-mm margin. Briefly, seven equidistant 6-MV beams (incident at angles of 50°, 80°, 150°, 180°, 210°, 280°, 310°) were used, and intensity-modulated beams were delivered using a dynamic multileaf technique. A dose of 60 Gy was delivered to the FDG-PET positive lesions, while 54 Gy was prescribed to other PTV in 30 fractions simultaneously using SIB-IMRT technique. Dose-volume histogram analysis showed that the mean dose delivered to the PTV was 61.2 Gy. The maximal doses to the spinal cord and duodenum were 50.2Gy and 49.6Gy, respectively. The mean doses to the pancreas, left kidney and right kidney were 31.8Gy, 10.6 Gy and 12.6 Gy, respectively, indicating within tolerance doses to those tissues.

Acute toxicity, evaluated according to the Common Terminology Criteria for Adverse Events Version 3.0, was only grade 1 anorexia. There was no neurological adverse effect induced by the IMRT. AFP returned to the normal value, and AFP-L3 fraction also fell to an undetectable level two months after the radiotherapy. The patient has no signs of elevated serum markers and growth of the residual mass with negative PET examination (Fig.3) 3 years after the salvage radiation.

## Discussion

To our knowledge, this is the first report of NSGCT successfully treated by IMRT. The clinical course of this case suggested the possibility of curative radiation therapy for NSGCT despite previous reports showing poor response.

Kersh, et al. showed that radiation therapy with a mean dose of 40 Gy was effective in patients with seminomas, but not in those with NSGCT [4]. However, no clinical study of radiation therapy for NSGCT with doses of more than 60 Gy, which is generally considered to be curative for solid tumors, has been reported. One previous case report showed that occult lumbar vertebral body metastasis of NSGCT was eradicated by radiation with a total dose of 61Gy [5], suggesting that dose escalation could be correlated with good outcome in NSGCT as well as prostate cancer [6]. Meanwhile, dose

escalation is generally limited by severe complication resulting from damages to the surrounding organs. IMRT contributes not only to dose escalation to the target lesions but also to reduction in toxicity because it works to conform to the shape of the target lesions minimizing radiation dose to surrounding normal tissues. This suggests that IMRT could be a valuable tool for treating retroperitoneal tumors surrounded by important intraperitoneal organs. Actually, IMRT has been applied to less radio-sensitive tumors such as head and neck sarcoma or melanoma than NSGCTs through its advantages of local dose escalation and limited toxicity [7]. In our case, dose escalation by using IMRT could contribute to local control of the residual tumor.

The feature in our case was sole elevation of AFP. This suggests the possibility that the residual tumor was teratoma which was more radiosensitive than other NSGCTs [4,8,9,10]. However, limitation in our case was no pathological evidence of the residual tumor because resection of the tumor was impossible. Therefore, it remains to be elucidated whether radiotherapy have equivalent efficacy for patients with elevation of AFP.

In conclusion, for localized residual tumors after salvage chemotherapy, high dose salvage radiation therapy by using IMRT might be an alternative treatment option to salvage surgery.



## References

1. Williams SD, Birch R, Einhorn LH, Irwin L, Greco FA, Loehrer PJ. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. *N Engl J Med* 1987; 316: 1435-40
2. Schmoll HJ, Souchon R, Krege S, Albers P, Beyer J, Kollmannsberger C, et al. European consensus on diagnosis and treatment of germ cell cancer: a report of the European Germ Cell Cancer Consensus Group (EGCCCG). *Ann Oncol* 2004; 15: 1377-99
3. Geldart TR, Gale J, Mckendrick J, Kirby J, Mead G. Late relapse of metastatic testicular nonseminomatous germ cell cancer: surgery is needed for cure. *BJU Int* 2006; 98: 353-8
4. Kersh CR, Constable WC, Hahn SS, Spaulding CA, Eisert DR, Jenrette JM, et al. Primary malignant extragonadal germ cell tumors. An analysis of the effect of radiotherapy. *Cancer* 1990; 65: 2681-85
5. Kanto S, Tokuyama S, Numahata K, Nakagawa H, Saito S, Arai Y. Occult lunbar

vertebral body metastasis of non-seminomatous germ cell tumor eradicated by radiation and salvage surgery 9years after initial onset. Nippon Hinyokika Gakkai Zasshi 2007; 98: 634-7

6. Staffurth J; Radiotherapy Development Board. A review of the clinical evidence for intensity-modulated radiotherapy. Clin Oncol 2010; 22: 643-57
7. Heudel P, Biston MC, Fayette J, Ramade A, Gassa F, Pommier P. Head and neck sarcoma: report of a case treated by intensity-modulated radiation therapy Int J Clin Oncol 2010; 15: 305-9
8. Albers P, Ganz A, Hannig E, Miersch WD, Müller SC. Salvage surgery of chemorefractory germ cell tumors with elevated tumor markers. J Urol 2000; 164: 381-4
9. Kobayashi T, Kawakita M, Terachi T, Habuchi T, Ogawa O, Kamoto T. Significance of elevated preoperative  $\alpha$ -fetoprotein in postchemotherapy residual tumor resection for the disseminated germ cell tumors. J Surg Oncol 2006; 94: 619-23
10. Aoyama H. Radiation therapy for intracranial germ cell tumors. Prog Neurol Surg 2009; 23: 96-105

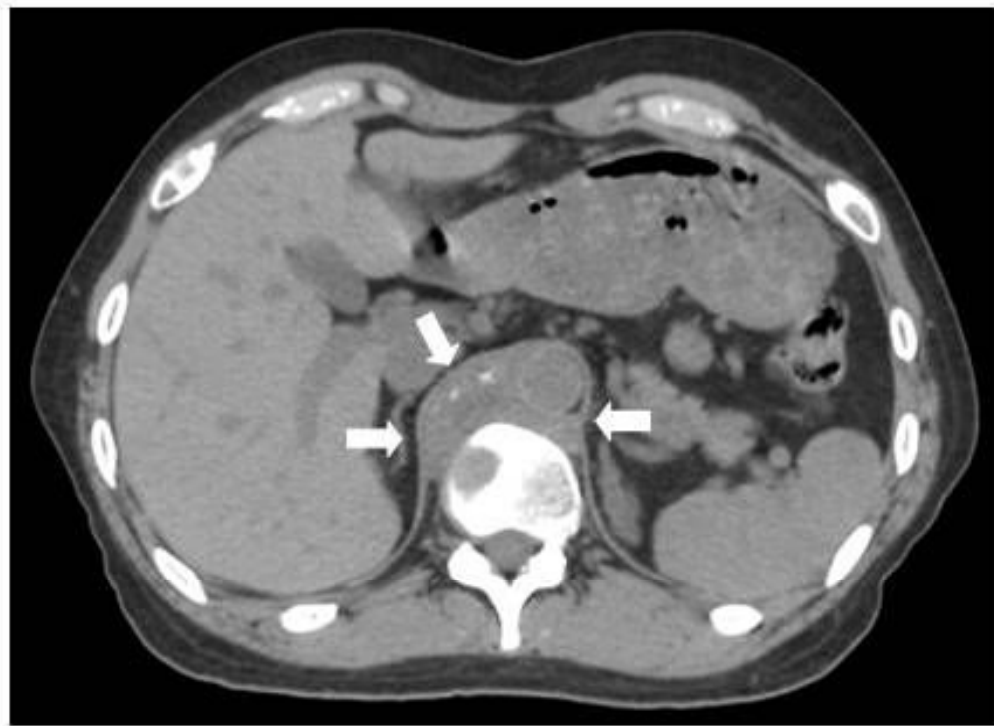


Fig.1a

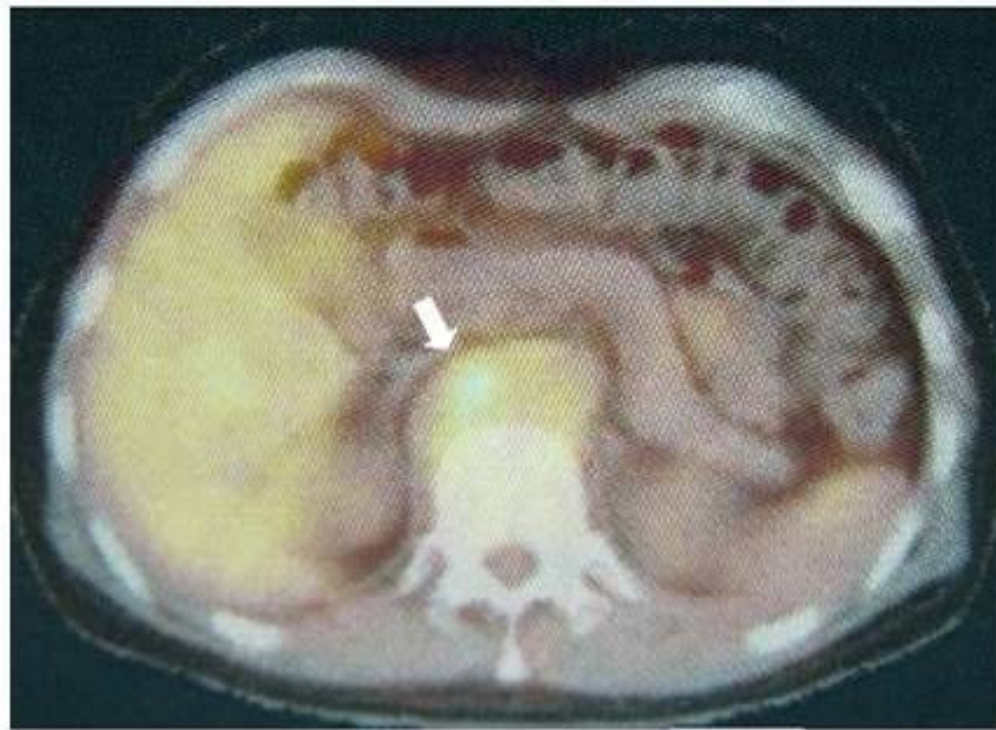


Fig.1b

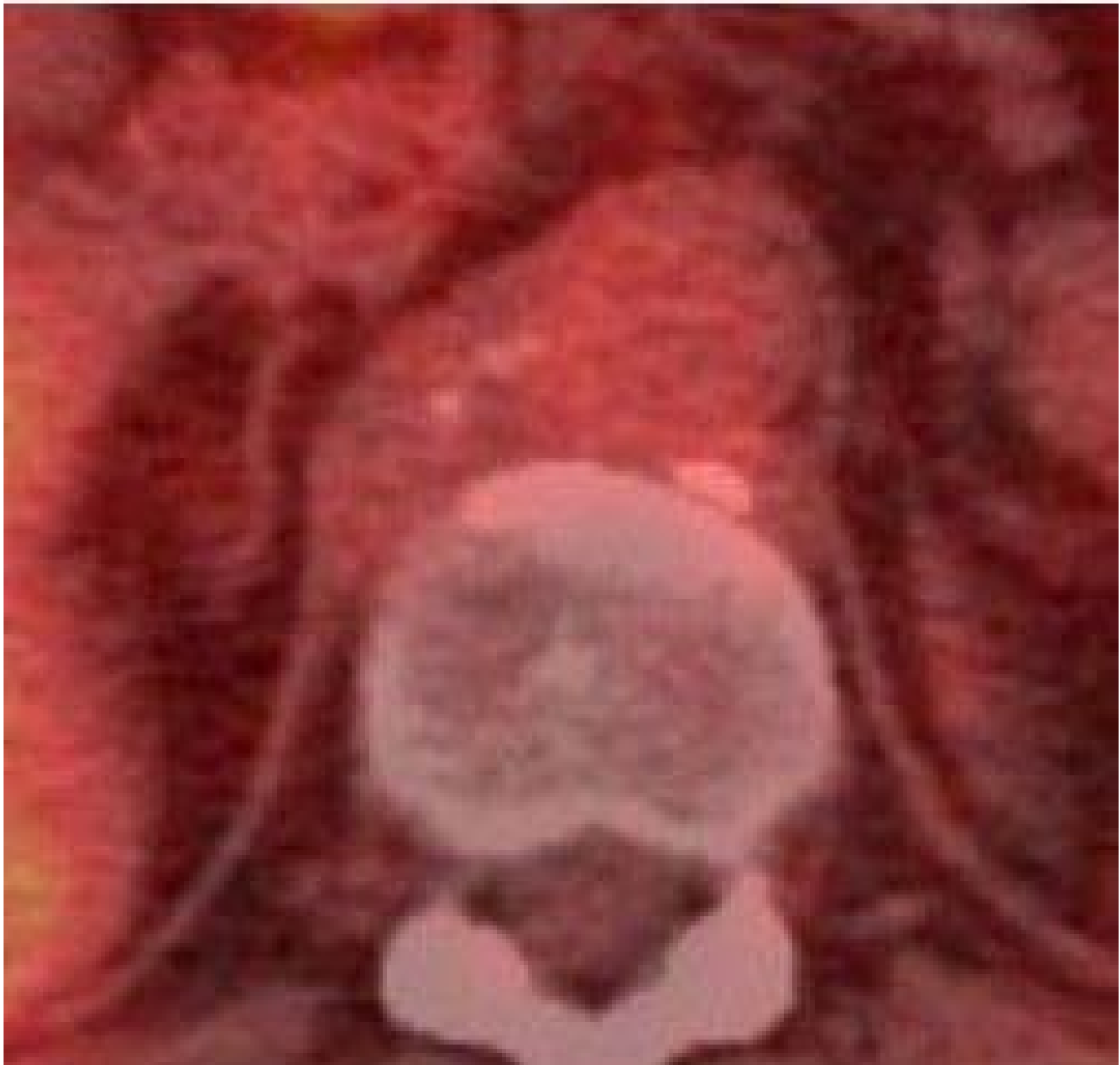


Fig.3

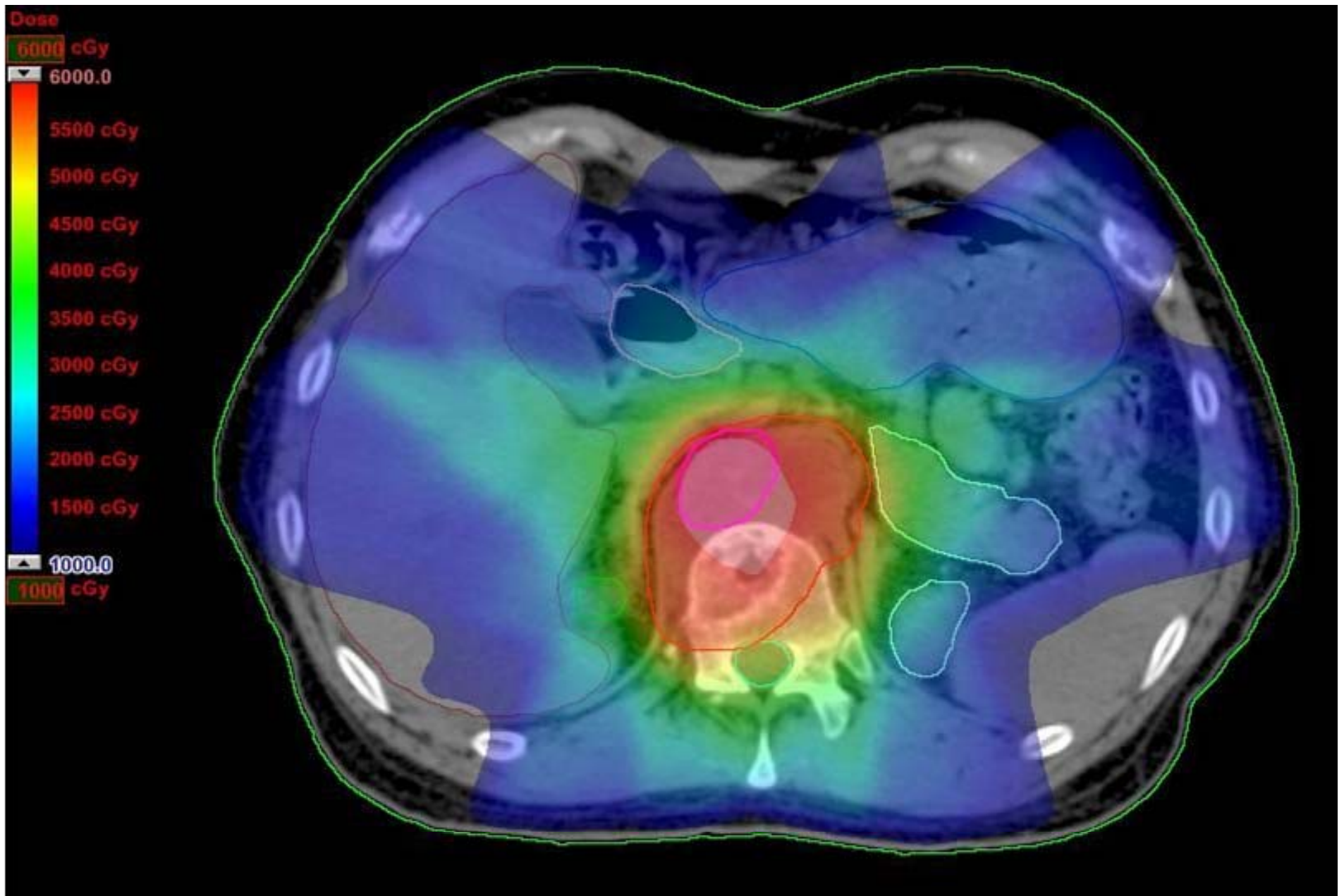


Fig.2