

CASE REPORTS

Cardiotoxicity of Multimodal Treatment for Breast Cancer

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Abstract

Introduction: Cardiac toxicity remains an important short and long term side effect of the anticancer therapy, impacting the quality of life and overall survival. **Objective:** To assess the cardiac toxicity of chemotherapy, trastuzumab treatment and radiotherapy and to highlight the effect and added risk of conventional vs conformal radiotherapy. **Materials and methods:** We present the case of a 31-years old female patient with stange III A left side breast cancer. The patient underwent neoadjuvant chemotherapy followed by left breast mastectomy, adjuvant chemotherapy, trastuzumab treatment and radiotherapy. After this treatment, she experienced a cardiac event evidenced by clinical symptoms and paraclinical examinations. **Conclusions:** In order to reduce the cardiac toxicity caused by the oncological treatment, a better understanding of the incriminating factors and proper monitoring is required.

Keywords: cardiac toxicity, breast cancer, chemotherapy, trastuzumab, radiotherapy

Rezumat

Introducere: Toxicitatea cardiacă rămâne un efect secundar important, precoce și tardiv, în urma tratamentului oncologic, cu impact asupra calității vieții și a supraviețuirii. **Obiectivul:** Evaluarea toxicității cardiace în urma chimioterapiei, a tratamentului cu trastuzumab și a radioterapiei, și evidențierea efectelor și riscurilor radioterapiei convenționale, comparativ cu radioterapia conformațională. **Materiale și metode:** Prezentăm cazul unei paciente în vârstă de 31 ani, diagnosticată cu cancer de sân stâng, stadiul III A. Pacienta a efectuat chimioterapie neoadjuvantă, mastectomie, chimioterapie adjuvantă, tratament cu trastuzumab și radioterapie. În continuare, aceasta a prezentat evenimente cardiace, evidențiate de simptomatologie clinică și examinări paraclinice. **Concluzii:** Pentru a reduce toxicitatea cardiacă în urma tratamentului oncologic, este necesară o mai bună înțelegere a factorilor incriminatori, precum și o monitorizare adecvată.

Cuvinte cheie: toxicitate cardiacă, cancer de sân, chimioterapie, trastuzumab, radioterapie.

INTRODUCTION

In the era of the optimal and the personalized oncological treatments, life expectancy increases, therewith the need of understanding and managing side effects is a challenging task.

The most notable research advances in breast cancer involve new radiation treatments techniques and targeted therapies.

Cardiac toxicity following radiotherapy (RT) is recognized as an important issue. Furthermore, with the prevalent and necessary treatment with anthracyclines and trastuzumab, which carry an independent and confirmed risk of cardiotoxicity¹⁻³ the additional heart disease risk following radiotherapy must be kept to a minimum.

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CASE PRESENTATION

We report the case of a 31-years old female patient diagnosed in October 2014 with stage III A (cT3 cN2 M0) left side breast cancer. The histopathological and immunohistochemistry results after excisional biopsy were: cribriform carcinoma associated with comedo-carcinoma and the invasion of fat tissue, G3, molecular profile of human epidermal growth factor 2 (HER 2), positive, estrogen receptors (ER) 98%, progesterone receptors (PGR) 1% and Ki67 20%.

Written informed consent for all types of the oncological treatment was obtained from the patient.

Before starting chemotherapy, cardiac examination was performed. The electrocardiography (EKG) showed a heart rate of 68/min, QRS axis +65 degrees, negative T waves in V1-V3 and transthoracic echography evidenced no pulmonary hypertension, an interatrial sept aneurism of 23 millimeters with no visible shunt, normal systolic function of the left ventricle and LVEF of 58%.

Between November 2014 and January 2015, the patient underwent neoadjuvant treatment consisting in 4 cycles of chemotherapy type FEC (5-Fluorouracil 500 mg/m² day 1, Epirubicin 75 mg/m² cycle 1 and afterwards 100 mg/m² and Cyclophosphamide 500 mg/m², every 3 weeks), with no cardiac side-effects but with grade 1 hematological toxicity, followed by modified radical mastectomy and axillar lymphadenectomy in February 2015. The histopathological examination described ductal cell carcinoma in 1 positive subcapsular axillary lymph node out of 4 nodes examined.

Between March 2015 and May 2015, the patient underwent adjuvant chemotherapy consisting in 4 cycles of Docetaxel (100 mg/m² day 1, every 3 weeks). As side effects, we mention grade 4 leukopenia and neutropenia after the first cycle of Docetaxel. Then, we recommended G-CSF. The cardiac examination from June 2015 at the initiation of the treatment with trastuzumab (8 mg/kgc day 1 initial dose followed by 6 mg/kgc day 1, every 3 weeks, for 1 year) consisted in EKG which showed few changes from November 2014 (negative T waves in V1-V4 and QRS axis at + 60 degrees) and the transthoracic echography showed LVEF of 58% with no other pathological changes.

Then, in June 2015, the patient underwent computed tomography (CT) simulation after proper supine positioning and immobilization for EBRT on a 15 degrees chest board. Conformal (3DCRT) radiotherapy was taken into consideration over conventional (2D) radiotherapy. The contouring was performed using Eclipse® treatment planning system (TPS; Varian Medical

Systems Inc., Palo Alto, CA). Contouring was performed on each CT image. The cardiac examination from July 2015 before radiotherapy consisted EKG which was similar with the one performed before neoadjuvant chemotherapy and transthoracic echography which described normal dimensions of left-side ventricle, LVEF of 55%, mobile narrow interatrial sept in the medium third without visible shunt, normal dimensions and functions of the right-side ventricle and atriums.

The organs at risk (OAR) that were assessed included the two lungs, the contralateral breast, the esophagus, the spinal cord, the thyroid, the heart, the two major coronary arteries, left coronary artery (LCA), right coronary artery (RCA), and the branches of the left main coronary artery: the anterior circumflex artery (ACX) and the left anterior descendent artery (LAD). The clinical target volume (CTV) consisted of the chestwall from the caudal border of the clavicle head to the loss of the CT apparent contralateral breast. The planning target volume (PTV) included the CTV and an additional margin of 5 mm. The delineation was performed by a radiation oncologist with the help of a radiologist and also using the heart atlas proposed by Feng et al.⁴. Conformal beams were designed and dose distribution was analyzed to provide the best dose coverage to PTV while sparing OARs using the dose volume histogram (DVH) of the outlined structured.

Between July and August 2015, the patient underwent EBRT to a total dose of 50,4 Gy with 1,8 Gy /fraction, one fraction per day.

In late September 2015 the patient describes an episode of heart palpitation and tachycardia while resting, accompanied by dizziness. The following cardiac examination, transthoracic echography and EKG de-

Table 1. Doses received by heart and heart arteries in 3D raditherapy vs 2D radiotherapy

	3D	2D
Heart D _{max}	43,8 Gy	45,93 Gy
Heart D _{med}	4,4 Gy	11,45 Gy
Heart V25	6,59	23,57
Heart V30	5,25	21,85
LCA D _{max}	1,68 Gy	3,29 Gy
LCA D _{med}	1,42 Gy	2,81 Gy
RCA D _{max}	1,39 Gy	3,55Gy
RCA D _{med}	1,29 Gy	3,22 Gy
ACX D _{max}	1,7 Gy	3,07 Gy
ACX D _{med}	1,36 Gy	2,54 Gy
LAD D _{max}	43,67 Gy	45,53 Gy
LAD D _{med}	19,36 Gy	38,34 Gy

D_{max}: maximum dose; D_{med}: median dose; V25 Heart: percentage (%) value of Heart receiving 25 Gy; V30 Heart: percentage (%) value of Heart receiving 30 Gy.

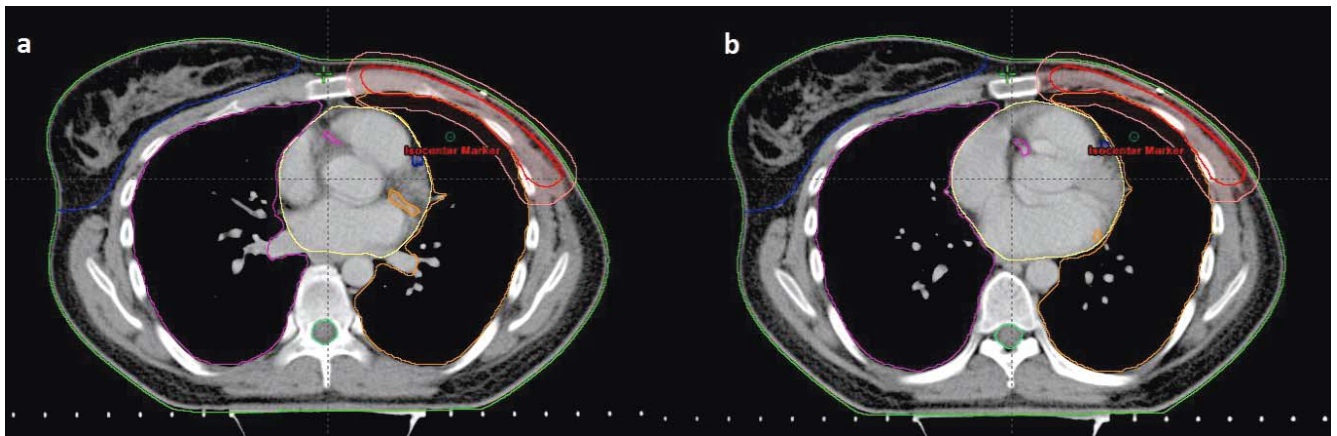


Figure 1. Transversal CT scans (A, B) featuring the the coronary arteries: ACX (orange), LAD (dark blue) and RCA (magenta).

scribes a 50% LVEF with a 5% reduction compared to mid-July examination with mild, diffuse hypokinesia; diastolic dysfunction with relaxing alteration, a heart rate of 70/min, QRS axis +60 degrees and deep negative T waves symmetrical in V2-V5, DI, AVL. Biological levels of the troponine I was 0,003 ng/ml and of N-terminal pro b-type natriuretic peptide (NT pro BNP), 141 pg/ml.

Due to the cardiac events which appeared, we decided to stop for 1,5 months the treatment with trastuzumab.

In November 2015, the cardiac examination, transthoracic echography and EKG showed an increase in LVEF from 50%, in September, to 57%, normal diastolic function, stationary EKG aspect. So, we continued the treatment with trastuzumab up to 1 year, well

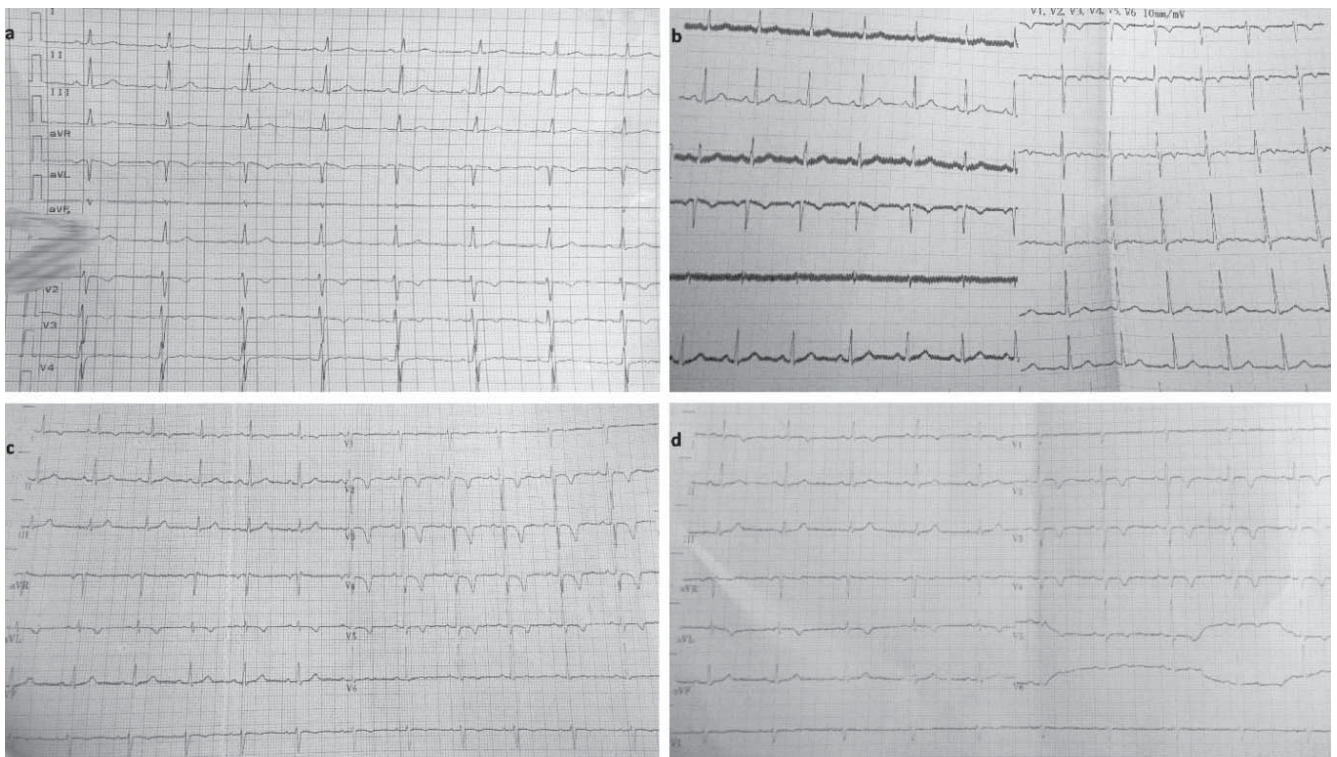


Figure 2. Electrocardiograms of the patient (A) prior to chemotherapy in November 2014, (B) June 2015 before starting trastuzumab, (C) immediately after the cardiac incident, three months after trastuzumab initiation and one and a half months after radiotherapy, in late September 2015 and (D) two months after the cardiac incident; November 2015.

tolerated and with close cardiac monitoring at every 3 months. In present, the patient is under hormonal treatment.

DISCUSSION

Cardiac toxicity remains an important side-effect of anticancer therapy so the increase in life-expectancy due to multimodal treatment might be negated by the increased mortality due to heart morbidity including myocardial dysfunctions, myocardial ischemia, arrhythmias, hypertension, thromboembolism^{5,6}. Early and accurate detection of cardiac injury is crucial.

According to ESMO guidelines, adverse cardiovascular effects after chemotherapeutic agents might include congestive heart failure for anthracyclines, cyclophosphamide and trastuzumab, ischemia or thromboembolism for antimetabolites (fluorouracil), hemorrhagic myocarditis (rare) for cyclophosphamide in high dose therapy⁷.

Usually, cardiac events due to trastuzumab manifest during treatment⁸, as in the case presented above. Cardiotoxicity due to trastuzumab is not a cumulative-dose related and it is highly reversible because it has been shown that in almost 1.5 months after the removal of trastuzumab from the treatment scheme, LVEF returns to baseline^{8,9}.

This patient had none of the most common risks factors responsible to trastuzumab related cardiac events: lower LVEF at baseline, older age, antihypertensive drugs¹⁰. Cardiac events appear especially when trastuzumab is administered after anthracyclines based chemotherapy¹¹. Moja. L. et al meta-analysis in Cochrane Database involving 8 studies with a total of 11991 patients that trastuzumab significantly increased the risk of congestive heart failure (CHF: RR 5.11; 90% CI 3.00 to 8.72, P < 0.00001); and left ventricular

ejection fraction decline (LVEF: RR 1.83; 90% CI 1.36 to 2.47, P = 0.0008)¹¹.

Furthermore, cardiac toxicity following left breast radiotherapy is recognized as an important issue. Clarke et al. highlighted this topic in a large study involving 42000 patients involving 78 randomized trials¹². It is well known that the number of left side breast cancer survivors is increasing. In addition, they may display adverse effects regarding cardiac and coronary toxicity and an important risk of mortality from heart disease (rate ratio 1.27), which is considered to be minor in the first 5 years, but then continues to develop even after 15 years (5,13). Although, the advances of the radiotherapy techniques in recent years have led to a decrease in heart and coronary dose irradiation, the long-term implications and benefits of these new techniques are not yet fully understood^{13,14}.

We wanted to assess the effect and added risk of the outdated breast conventional (2D) radiotherapy vs conformal (3D) radiotherapy, regarding the cardiac toxicity.

According to the Sarah et al. study involving 2168 women, the risk of a major coronary event increased linearly with the mean dose to the heart. The magnitude of the risk was 7.4% per gray, with the risk being noted on the first 5 years after exposure and continued for at least 20 years¹⁵.

Comparing DVH and dose distribution, there is a high difference between the two techniques regarding the dose received by the heart and the coronary arteries. The most notable difference regards the LAD artery, known to be involved in radiation-induced morbidity, being situated on the anterior surface of the heart and intersected by the radiation beam. It is known that damage to the LAD coronary is a common cause of

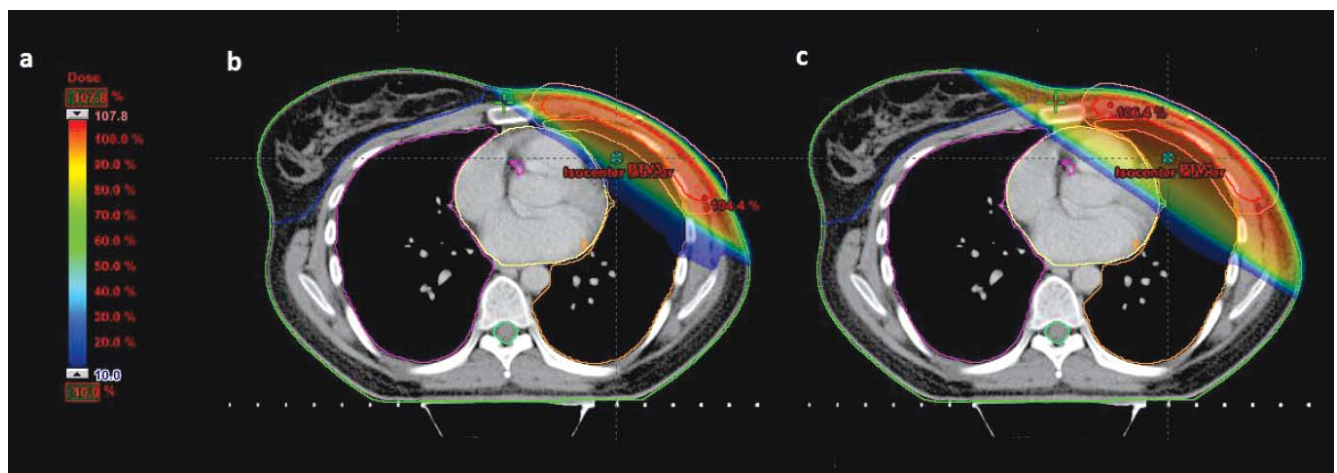


Figure 3. Transversal CT scans and evaluation of (A) dose distribution in; (B) conformal 3D radiotherapy vs (C) conventional 2D radiotherapy.

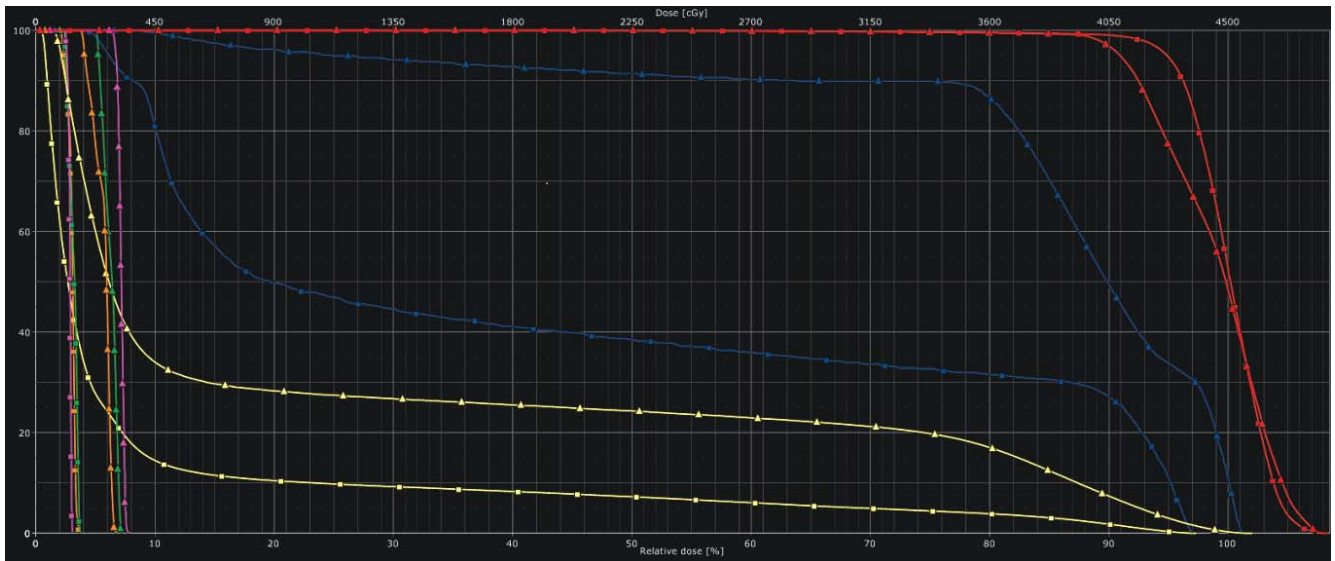


Figure 4. DVH of the treatment plan in 3D radiotherapy vs 2D radiotherapy: CTV (3D) —■—, CTV (2D) —▲—, Heart (3D) —■—, Heart (2D) —▲—, LCA (3D) —■—, LCA (2D) —▲—, RCA (3D) —■—, RCA (2D) —▲—, ACX (3D) —■—, ACX (2D) —▲—, LAD (3D) —■—, and LAD (2D) —▲—.

non-radiation induced myocardial infarction (MI) and it may also play a role in radiation induced MI^{16,17}.

We report the case of a young female patient diagnosed with left side breast cancer who has developed cardiac events during the oncological treatment. Likewise other studies, the cardiac event appeared when trastuzumab was administered after anthracyclines based chemotherapy¹⁰. Recent studies have indicated that the association of breast radiotherapy and trastuzumab is safe from the cardiac point of view because apparently they do not present cumulative risk¹⁸. Due to the fact that in the majority of the cases cardiac injury becomes symptomatic in years after oncological treatment, few studies have associated early rises in cardiac biomarkers levels with clinical endpoints¹⁹⁻²¹. However, there are

methods that can detect earlier a significant cardiac toxicity, such as the NT- proBNP biomarker, but further analyses of a large number of cases are warranted to evaluate the clinical significance of this approach.

CONCLUSION

There is a strong need for close monitoring and discovering possible side effects in patients with breast cancer treated with multimodal therapy.

It is important to consider minimizing cardiac irradiation doses as well as best tumor control when making decisions about the use of radiotherapy for breast cancer. If possible, individualization of radiotherapy techniques should be performed to reduce the additional cardiac toxicity in the long term.

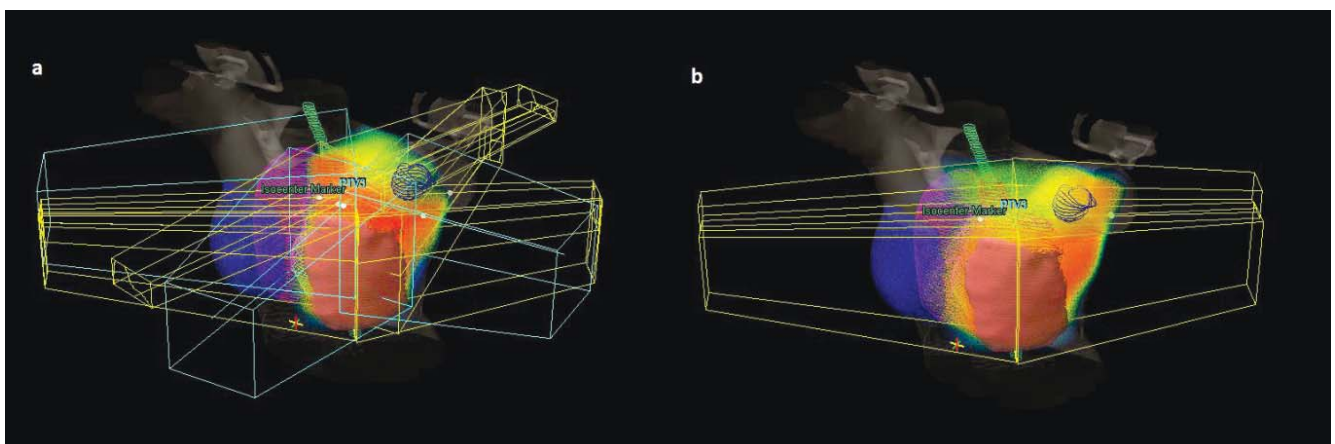


Figure 5. (A) 3D fields and set-ups vs (B) 2D fields.

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