Pediatric Radiology

Imaging of Late Complications of Cancer Therapy in Children

--Manuscript Draft--

Manuscript Number:	PRAD-D-16-00221R1
Full Title:	Imaging of Late Complications of Cancer Therapy in Children
Article Type:	Review
Funding Information:	
Abstract:	Long-term survival after childhood cancer has improved dramatically over recent decades, but survivors face lifelong risks of adverse health effects. Many of these chronic conditions are a direct result of previous therapeutic exposures. Compared to their siblings, survivors face a greater than eight fold increase in relative risk of severe or life-threatening medical conditions; the most significant of these include second malignancies, cardiovascular and pulmonary diseases. Imaging can play a key role in both identifying and characterising such complications, which can be reasonably predicted with knowledge of the type of treatment received. This article highlights the varied radiological presentations and features seen in late cancer therapy-related conditions.
Corresponding Author:	Govind Babusing Chavhan, MD, DNB, DABR The Hospital for Sick Children Toronto, Ontario CANADA
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	The Hospital for Sick Children
Corresponding Author's Secondary Institution:	
First Author:	Susan Shelmerdine
First Author Secondary Information:	
Order of Authors:	Susan Shelmerdine
	Govind Babusing Chavhan, MD, DNB, DABR
	Paul Babyn, MD
	Paul Nathan, MD
	Sue Kaste, DO
Order of Authors Secondary Information:	
Author Comments:	To Peter Strouse, MD Editor, Pediatric Radiology Ref: MS# P-RAD-16-00221 Dear Dr. Strouse, Thank you very much for allowing us to submit revised manuscript on "Imaging of late complications of cancer therapy in children" (MS# 16-00221). We thank reviewers and the editor for their valuable comments. Please find attached a detailed response to comments from you and the reviewers on the following pages. These have been incorporated into the manuscript as tracked changes. We sincerely hope that you will find this revised manuscript suitable for publication. Thanking you Yours sincerely, Govind B. Chavhan, MD

Powered by Editorial Manager® and ProduXion Manager® from Aries Systems Corporation

Review

Imaging of late complications of cancer therapy in children

Susan C. Shelmerdine[1]

Govind B. Chavhan[1]

Paul S. Babyn[2]

Paul C. Nathan[3]

Sue C. Kaste[4,5]

CME activity
This article has been selected as the CME activity for the current month. Please visit the SPR Web site at www.pedrad.org on the Education page and follow the instructions to complete this CME activity.

✉ Govind B. Chavhan
drgovindchavhan@yahoo.com

[1]Department of Diagnostic Imaging,
The Hospital for Sick Children and University of Toronto,
555 University Ave., Toronto, ON M5G 1X8, Canada

[2] Department of Medical Imaging, Royal University Hospital,
Saskatoon, SK, Canada

[3] Division of Hematology/Oncology, Department of Pediatrics,
The Hospital for Sick Children and University of Toronto,
Toronto, ON, Canada

[4] Department of Diagnostic Imaging and Department of Oncology,
St. Jude Children's Research Hospital, Memphis, TN, USA

[5] Department of Radiology,
University of Tennessee School of Health Sciences, Memphis,
Memphis, TN, USA

Blinded Manuscript Click here to view linked References

Abstract

Long-term survival after childhood cancer has improved dramatically over recent decades but survivors face lifelong risks of adverse health effects. Many of these chronic conditions are a direct result of previous therapeutic exposures. Compared to their siblings, survivors face a greater than 8-fold increase in relative risk of severe or life-threatening medical conditions; the most significant of these include second malignancies and cardiovascular and pulmonary diseases. Imaging can play a key role in identifying and characterizing such complications, which can be reasonably predicted with knowledge of the child's treatment. This article highlights the varied radiologic presentations and features seen in late cancer-therapy-related conditions.

Keywords Cancer therapy, Children, Computed tomography, Late effects, Magnetic resonance imaging, Radiography, Toxicities

Introduction

Long-term survival after childhood cancer has improved dramatically over recent decades, with 5-year survival rates ranging from 64% to 97% [1] compared to 45% in the mid-1970s [2]. Despite such encouraging statistics, survivors face an increased lifelong risk of adverse health effects [3, 4], many of which stem directly from their previous therapeutic exposures [5]. Results from the Childhood Cancer Survivor Study (CCSS) have shown that compared with their siblings, survivors face an 8.2-fold increased relative risk for a severe or life-threatening condition, with cumulative incidence of chronic conditions reaching 73.4% at 30 years after diagnosis [6].

The late effects can affect all organ systems (Table 1), but the most severe conditions include second malignancies and cardiovascular and pulmonary diseases [7–10]. The

Children's Oncology Group (COG) has developed risk-based, exposure-related guidelines for follow-up care in childhood cancer survivors [11]. Radiology plays a key role in both identifying and characterizing complications, most of which can be reasonably predicted with knowledge of the type of treatment received [12].

This article serves as a companion piece to our review on acute and subacute toxicities of cancer therapies in children [13]. This article highlights the radiologic appearances of late cancer-therapy-related, non-neurological conditions, defined as those occurring at least 1 year after the conclusion of therapy. Some complications, although not strictly diagnosed by imaging, are also described for their secondary radiologic features. Table 1 provides a general overview of the various organ systems involved, and the more commonly seen entities are described in further detail in this article.

Multisystem complications

Chronic graft-versus-host disease

Allogenic hematopoietic stem cell transplantation (HSCT) is a well-established treatment for some hematologic malignancies [14]. The incidence of chronic graft-versus-host disease (GVHD) following HSCT in children ranges from 6% when the stem cells are infused from a matched sibling to 65% when they are provided by a matched unrelated donor [15]. Chronic GVHD is no longer defined based on the time after HSCT (historically, >100 days after transplantation), but according to specific clinical and functional criteria that suggest immune dysfunction, none of which relies upon imaging features [16]. The median onset of chronic GVHD after HSCT is approximately 6 months and onset is usually not seen after 3 years post-transplantation [16]. Acute GVHD typically involves skin, liver and gastrointestinal tract. However, chronic GVHD can involve any organ system. Imaging manifestations of chronic GVHD include gastrointestinal strictures, findings that mimic primary sclerosing cholangitis (PSC) and bronchiolitis obliterans [17]. Although PSC-like changes have been

described in experimental chronic GVHD in a mice model [18], this has not been reported in children (Fig. 1). It is estimated that 80% of people with chronic GVHD have liver involvement [19] and if a biopsy is required to confirm diagnosis, an interventional radiologist might be asked for assistance.

Second malignant neoplasms

Second malignant neoplasms are defined as "histologically distinct malignancies developing after completion of treatment for the primary malignancy" [20]. They are the most frequent cause for non-relapse late mortality in survivors [21], who have a 3- to 6-fold increased risk of malignancy compared to the general population [22]. The risk of developing a second malignant neoplasm has been estimated to be 10% at 20 years and 26% at 30 years age [23], although this risk varies with the type of primary cancer diagnosis (there is a higher risk in hereditary retinoblastoma [24] and Hodgkin lymphoma survivors [25]), therapy received and underlying genetic predisposition (e.g., Li–Fraumeni syndrome).

Post-treatment solid tumors are more strongly associated with radiation therapy, whereas those associated with chemotherapy (typically alkylating agents or topoisomerase II inhibitors) include myelodysplasia and acute myeloid leukemia [26]. Solid second malignant neoplasms include breast (the most common second malignant neoplasm in the CCSS cohort [27]), thyroid, brain and bone tumors [22] (Fig. 2). In general, the higher the radiation dose received and the younger the age at treatment, the greater the risk for developing solid second malignant neoplasms.

Imaging is used for surveillance in selected subgroups such as those with a cancer predisposition syndrome [28]. Whole-body MRI is a radiation-free technique to screen for these neoplasms. Periodic whole-body MRI might be performed in children with Li–Fraumeni syndrome for development of any neoplasm because they are predisposed to cancer

development [28]. Girls who get chest radiation are at increased risk for subsequent breast cancer. The Children's Oncology Group recommends initiation of screening MRI/mammography at age 25 or 8 years after radiation, whichever is later [12].

Endocrine dysfunction

Thyroid

The thyroid gland may be included within the radiation field when treating head and neck tumors, or during cranio-spinal irradiation. Hypothyroidism is the most common thyroid disorder following radiotherapy [29] and can also occur after HSCT [30]. However, even when this condition is present, the thyroid gland can still look normal on sonography. Histopathological changes of an irradiated thyroid gland include follicular degeneration, stromal atrophy and obliteration of underlying vasculature [31]. Sonographic features of the irradiated thyroid gland can include diffuse atrophy, solitary or multiple nodules (which may be malignant), cysts (simple and complex) and heterogeneity within the thyroid tissue [32] (Fig. 3). Differentiating malignant from benign nodules sonographically can be difficult, but features concerning for malignancy include the presence of microcalcifications and irregular margins, and absence of a uniform hypoechoic halo around the nodule [33]. Even though a hypoechoic halo has 95% specificity for a benign thyroid nodule, a halo is not seen in >50% of benign nodules [33]. Also, 10–24% of papillary thyroid carcinomas have either a complete or incomplete halo around them [33].

Growth

Cranial irradiation can damage the hypothalamic-pituitary axis, leading to gonadotropin or growth hormone deficiency at high dosages, and precocious puberty at lower dosages [34-37]. The age of pubertal onset has been shown to be particularly important in determining final height, with younger children being at greater risk of developing precocious puberty and

therefore eventual shorter stature [38]. Growth hormone deficiency can be seen in children who received total body irradiation in preparation for bone marrow transplantation [39]. The radiologist might be asked to review a child's bone age to determine the degree of bone delay or advancement. Knowledge of this late effect can also be helpful to the radiologist reviewing a skeletal survey for short stature.

Pulmonary complications

Significant long-term pulmonary dysfunction, as determined by pulmonary function tests (PFT), can be seen in survivors after therapy [40, 41]. These effects are more likely to occur if children receive both chemotherapy and radiation, and can be seen in up to 72% of cases [26]. Pulmonary late effects include pulmonary fibrosis, interstitial pneumonitis, and restrictive/obstructive lung diseases. In children surviving 5 years or more, the CCSS [42] found a significant association between cancer therapy and lung fibrosis, recurrent pneumonia and pleurisy. The strongest association of pulmonary damage was demonstrated between radiotherapy and pulmonary fibrosis. However, pulmonary toxic chemotherapy agents such as bleomycin, busulfan, lomustine (CCNU [1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea]) and carmustine (BCNU [bis-chloroethylnitrosourea]) also contributed to developing fibrosis. Chest CT is useful for detecting pulmonary fibrosis, bronchiolitis obliterans and bronchiolitis obliterans organizing pneumonia (BOOP). Pulmonary fibrosis involves the part of the lung included in the radiation field (Fig. 4). Typical fibrotic changes can be seen in the medial aspects of both lungs in Hodgkin lymphoma survivors who received mediastinal radiation. Non-pulmonary findings, such as simple thymic cysts, can also occur as a result of chemotherapy or radiation. If large, these can mimic tumor recurrence [43].

Cardiovascular complications

Congestive cardiac failure and cardiomyopathy are well-recognized complications from prior anthracycline chemotherapy or chest radiation [44]. This is of particular concern because approximately 60% of survivors might have been exposed to one of these therapies [10]. They face a 15-fold increased risk of heart failure [6] compared to the general population. The condition is progressive and can be clinically silent for years [45]. For this reason several oncology groups worldwide advocate lifelong screening with echocardiography and clinical assessment every 1–5 years, depending on cumulative anthracycline dose exposure, radiation to a field that included the heart, and age at therapy [46]. Chest radiographs might demonstrate cardiomegaly with or without signs of cardiac failure (Fig. 5), but the imaging modality of choice for screening for cardiomyopathy is echocardiogram.

Gastrointestinal complications

Enteric

Chronic radiation enteropathy typically occurs 6–24 months post radiotherapy [31]. It can manifest as mucosal ulceration, stricture formation, malabsorption or bowel obstruction [47] (Fig. 6); the last is reported to occur in 36% of survivors [48].

Surgical intervention for the primary malignancy can also result in subsequent adhesion formation. If resection of previously irradiated bowel is later needed, there is a high incidence of anastomotic dehiscence, re-obstruction and even mortality [49].

Esophageal strictures (Fig. 7) and acquired tracheoesophageal fistulas can also be seen in children treated with radiation or chemotherapy [50]. However, these are rare and more commonly associated with non-malignant causes, like foreign body ingestion, severe mucositis and candida esophagitis [51, 52].

Hepatobiliary

Focal nodular hyperplasia

Focal nodular hyperplasia (FNH) is a non-malignant entity seen with increasing frequency in children following treatment with chemotherapy, HSCT or radiation [53–55]. The interval between cancer diagnosis and discovery of FNH ranges 2–12 years with median interval of 6.7 years [56]. A liver lesion might initially be identified on sonography but FNH can be diagnosed with greater confidence and accuracy by liver MRI [57] (Fig. 8). FNH in cancer survivors tends to be multiple, small (<3 cm) and atypical, with lack of a central scar. The use of MRI with hepatocyte-specific contrast media like gadobenate helps to differentiate FNH from metastases [58].

Hemochromatosis

Iron overload is common in cancer survivors who have received multiple red blood cell transfusions and is associated with hepatic, cardiac and endocrine dysfunction. Siderosis can be histologically identified in up to 70% of children near the end of their treatment for acute lymphoblastic leukemia [59–61], and hepatic iron overload can be reliably diagnosed and approximately quantified by MRI [62–64] (Fig. 9).

Hepatosteatosis

Fatty infiltration of the liver can occur for several reasons in childhood cancer survivors, such as from immunosuppressive chemotherapeutic agents; in survivors of hepatoblastoma treated with liver transplantation [65], or as part of a metabolic syndrome in cancer survivors secondary to late effects of hyperlipidemia, insulin resistance from total whole-body irradiation, and bone marrow transplantation [66]. Fatty infiltration results in increased echogenicity of the hepatic parenchyma on sonography. Fatty infiltration can be reliably diagnosed with in- and out-phase imaging on MRI.

Hepatobiliary toxicity

Limited data exist on late effects of chemotherapy on the liver but hepatobiliary dysfunction is thought to be related to prior anti-metabolite agent therapy (e.g., methotrexate, 6-mercaptopurine) and after HSCT [67]. Delayed hepatic injury might not be preceded by clinically apparent acute toxicity before leading to hepatic fibrosis. Fibrosis places the child at risk of developing portal hypertension, cirrhosis and hepatocellular carcinoma [68]. Radiation-induced hepatic damage is uncommon in cancer survivors unless predisposing conditions (e.g., viral hepatitis, iron overload) are present [69]. In our experience, nonspecific increased echogenicity and heterogeneity of hepatic parenchyma are commonly observed on US in cancer survivors, which could represent some form of hepatic damage.

Genitourinary system complications

Therapy-related late effects on kidneys include radiation nephropathy, renal atrophy (with focal or diffuse parenchymal and functional loss [70]; Fig. 10) and end-stage renal disease (ESRD) as a result of radiation or nephrotoxic chemotherapeutic agents (such as cisplatin [71] and ifosfamide [72]). These toxicities are generally observed 6 months or more after treatment [73].

Bladder fibrosis can develop from radiotherapy or chemotherapy (particularly cyclophosphamide), resulting in interstitial fibrosis of the bladder wall. Urgency and frequency from reduced bladder capacity are common symptoms. Imaging, though rarely used to make the diagnosis, might demonstrate a contracted and poorly distensible bladder, sometimes accompanied by hydronephrosis [74]. Fistula formation to adjacent bowel loops rarely occurs in children but is more common in adults after brachytherapy [70].

Gonadal dysfunction is the most severe long-term effect in cancer survivors, especially after alkylating agents and pelvic radiotherapy [64]. Hypothalamic-pituitary axis disorders also result in impaired fertility in cancer survivors [10, 75, 76]. Ovarian transposition outside the radiation field, usually superiorly in the abdomen, is sometimes performed prior to radiotherapy to minimize radiation damage to the ovaries in children with pelvic cancers [77] (Fig. 11).

Musculoskeletal complications

Bone growth deformity

Radiotherapy, chemotherapy and surgery have all been associated with long-term musculoskeletal effects independently and additively [78]. Radiation therapy can affect chondroblast and chondrocyte proliferation with reduction in bone growth; soft-tissue hypoplasia can also result. Scoliosis is thought to be sometimes caused by radiation-induced asymmetrical growth plate impairment (Fig. 12). Chances of spinal malalignment increase with younger age at exposure, higher doses, and asymmetrical radiation [78]. Bony hypoplasia, especially involving flat bones, can result from inhibition of osteogenesis by radiation [78]. Severe facial deformity has been noted in up to 30% of children who received radiation for head and neck rhabdomyosarcoma [79]. Growth disturbances affecting hips and pelvis include hemiatrophy of the pelvis (Fig. 13), slipped capital epiphyses (Fig. 14) and osteonecrosis of the femoral head. Other effects include leg-length discrepancy and muscular atrophy [78, 80, 81]. Radiographs play an important role in assessment of these abnormalities related to bone growth and could be sufficient in most cases.

Bone mineral density changes

Treatment with corticosteroids, methotrexate and radiotherapy has been implicated in altered bone remodeling [82] and reduction in bone mineral density, predisposing patients to

pathological fractures [30] (Fig. 15). The incidence of bone mineral density deficits may be as high as 45% in cancer survivors [83].

Radiation osteitis is typically witnessed 1 year after therapy [81] and can be difficult to differentiate from residual or metastatic bone disease. As irradiated bone heals, osteoid deposits can form, resulting in a coarsened trabecular matrix pattern with disorganized sclerosis (Fig. 16).

Bone tumors

Osteochondromas are the most common secondary bone tumor to develop within a radiation field. Their incidence is 1–2% in the general population but 6–20% in children treated with radiation therapy (Figs. 17 and 18). The propensity for malignant degeneration is rare and not thought to be greater than that in the general population [84, 85].

Radiation-induced bone sarcomas, in particular osteosarcomas, can develop in cancer survivors [86]. The risk increases significantly in children with cancer predisposition syndromes such as retinoblastoma and Li–Fraumeni syndrome. The mean latency period for developing malignant bone tumors is about 10 years [87]. The presence of an enhancing soft-tissue mass associated with bone destruction seen on MRI helps to differentiate second malignancy bone sarcoma from radiation changes and infections.

Other effects

Methotrexate-induced osteopathy radiographically appears very similar to scurvy, with osteoporosis, decreased mineralization and fractures [88]. Dense metaphyseal bands of long bones, within epiphyseal ossification centers, anterior rib ends, sternum and spine have been reported in children receiving pamidronate for bone pain in metastatic osteosarcoma [89].

Conclusion

The late effects of cancer therapy in children can affect all organ systems of the body and can cause early mortality. This article has highlighted many of the long-term sequelae that can be evaluated by imaging. With increase in long-term survival rates of childhood cancer patients, recognition of these radiologic findings is of vital importance to both pediatric and adult radiologists.

Compliance with ethical standards

Conflicts of interest None

References

1. Cancer in children. The American Cancer Society website http://www.cancer.org/cancer/cancerinchildren/detailedguide/cancer-in-children-treating-survival-rates. Accessed 15 November 2015
2. Howlader N, Noone AM, Krapcho M et al (2015) SEER cancer statistics review, 1975–2012, National Cancer Institute. Bethesda, MD http://seer.cancer.gov/csr/1975_2012. Accessed 21 November 2015
3. Reulen RC, Winter DL, Frobisher C et al (2010). Long-term cause-specific mortality among survivors of childhood cancer. JAMA 304:172–179
4. Aziz NM, Oeffinger KC, Brooks S, Turoff AJ (2006) Comprehensive long-term follow-up programs for pediatric cancer survivors. Cancer 107:841–848
5. Bhatia S (2012) Long-term complications of therapeutic exposures in childhood: lessons learned from childhood cancer survivors. Pediatrics 130:1141–1143
6. Oeffinger KC, Mertens AC, Sklar CA et al (2006) Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 355:1572–1582

7. Robinson LL, Hudson MM (2014) Survivors of childhood and adolescent cancer: life-long risks and responsibilities. Nat Rev Cancer 14:61–70
8. Oeffinger KC, Hudson MM (2004) Long-term complications following childhood and adolescent cancer: foundations for providing risk-based health care for survivors. CA Cancer J Clin 54:208–236
9. Schwartz CL, Hobbie WL, Constine LS, Ruccione KS (2005) Survivors of childhood and adolescent cancer, 2nd edn. Mosby, St. Louis, MO
10. Hudson MM, Ness KK, Gurney JG et al (2013) Clinical ascertainment of health outcomes among adults treated for childhood cancer. JAMA 309:2371–2381
11. Children's Oncology Group (2014) Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. http://survivorshipguidelines.org. Accessed 15 November 2015
12. Marina N (1997) Long-term survivors of childhood cancer: the medical consequences of cure. Pediatr Clin North Am 44:1021–1042
13. Chavhan GB, Babyn PS, Nathan PC, Kaste SC (2016) Imaging of acute and subacute toxicities of cancer therapy in children. Pediatr Radiol 46:9–20
14. Hollingsworth CL, Frush DP, Kurtzburg J, Prasad VK (2008) Pediatric hematopoietic stem cell transplantation and the role of imaging. Radiology 248:348–365
15. Baird K, Cooke K, Schultz KR (2010) Chronic graft versus host disease (GVHD) in children. Pediatr Clin North Am 57:297–322
16. Jagasia MH, Greinix HT, Arora M et al (2015) National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 21:389–401.e1

17. Coy DL, Ormazabal A, Godwin JD, Lalani T (2005) Imaging evaluation of pulmonary and abdominal complications following hematopoietic stem cell transplantation. Radiographics 25:305–317
18. Nonomura A, Kono N, Minato H, Nakanuma Y (1998) Diffuse biliary tract involvement mimicking primary sclerosing cholangitis in an experimental model of chronic graft-versus-host disease in mice. Pathol Int 48:421–427
19. Fisher VL (1999) Long-term follow-up in hematopoietic stem-cell transplant patients. Pediatr Transplant 3:122–129
20. Bhatia S, Constine LS (2005) Second malignant neoplasms. In: Halperin EC, Constine LS, Tarbell NJ, Kun LE (eds), Pediatric radiation oncology, 4th edn). Lippincott Williams & Wilkins, Philadelphia, pp 614–632
21. Leisenring WM, Mertens AC, Armstrong GT et al (2009) Pediatric cancer survivorship research: experience of the childhood cancer survivor study. J Clin Oncol 27:2319–2327
22. Bhatia S (2005) Cancer survivorship — pediatric issues. Hematology Am Soc Hematol Educ Program 2005:507–515
23. Bhatia S, Yasui Y, Robison LL et al (2003) High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. J Clin Oncol 21:4386–4394
24. Wong FL, Boice JD Jr, Abramson DH et al (1997) Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA 278:1262–1267
25. Metayer C, Lynch C, Clarke EA et al (2000) Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. J Clin Oncol 18:2435–2443

26. Bhatia S, Sklar C (2002) Second cancers in survivors of childhood cancer. Nat Rev Cancer 2:124–132
27. Neglia JP, Friedman DL, Yutaka Y et al (2001) Second malignant neoplasms in five-year survivors of childhood cancer: Childhood Cancer Survivor Study. J Natl Cancer Inst 93:618–629
28. Villani A, Tabori U, Schiffman J et al (2011) Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study. Lancet Oncol 12:559–567
29. Van Dorp W, van Beek RD, Laven JS et al (2012) Long-term endocrine side effects of childhood Hodgkin's lymphoma treatment: a review. Hum Reprod Update 18:12–28
30. Borgstrom B, Bolme P (1994) Thyroid function in children after allogeneic bone marrow transplantation. Bone Marrow Transplant 13:59–64
31. Friedman DL, Constine LS (2005) Late effects of cancer treatment. In: Halperin EC, Constine LS, Tarbell NJ, Kun LE (eds), Pediatric radiation oncology, 4th edn. Lippincott Williams & Wilkins, Philadelphia, pp 524–612
32. Soberman N, Leonidas JC, Cherrick I et al (1991) Sonographic abnormalities of the thyroid gland in longterm survivors of Hodgkin disease. Pediatr Radiol 21:250–253
33. Hoang J, Lee WK, Lee M et al (2007) US features of thyroid malignancy: pearls and pitfalls. Radiographics 27:847–865
34. Shalet SM, Brennan BM (2002) Puberty in children with cancer. Horm Res 57:39–42
35. Chemaitilly W, Merchant TE, Li Z et al (2016) Central precocious puberty following the diagnosis and treatment of paediatric cancer and central nervous system tumours: presentation and long-term outcomes. Clin Endocrinol 84:361–371

36. Barnes N, Chemaitilly W (2014) Endocrinopathies in survivors of childhood neoplasia. Front Pediatr 2:101
37. Chemaitilly W, Hudson MM (2014) Update on endocrine and metabolic therapy-related late effects observed in survivors of childhood neoplasia. Curr Opin Endocrinol Diabetes Obes 21:71–76
38. Shalet SM, Crowne EC, Didi MA et al (1992) Irradiation-induced growth failure. Baillieres Clin Endocrinol Metab 6:513–526
39. Davis NL, Stewart CE, Moss AD et al (2015) Growth hormone deficiency after childhood bone marrow transplantation with total body irradiation: interaction with adiposity and age. Clin Endocrinol 83:508–517
40. Tantawy AA, Elbarbary N, Ahmed A et al (2011) Pulmonary complications in survivors of childhood hematological malignancies: single-center experience. Pediatr Hematol Oncol 28:403–417
41. Huang TT, Hudson MM, Stokes DC et al (2011) Pulmonary outcomes in survivors of childhood cancers: a systematic review. Chest 140:881–890
42. Mertens AC, Yasui Y, Loiu Y et al (2002) Pulmonary complications in survivors of childhood and adolescent cancer: a report from the Childhood Cancer Survivor Study. Cancer 95:2431–2441
43. Borgna-Pignatti C, Andreis IB, Rugolotto S et al (1994) Thymic cyst appearing after treatment of mediastinal non-Hodgkin lymphoma. Med Pediatr Oncol 22:70–72
44. Lipshultz SE, Adams MJ, Colan SD et al (2013) Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions: a scientific statement from the American Heart Association. Circulation 128:1927–1995
45. Hunt SA, Abraham WT, Chin MH et al (2009) 2009 focused update incorporated into

the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines developed in collaboration with the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 53: e1–e90

46. Armenian SH, Hudson MM, Mulder RL et al (2015) Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol 16:e123–36
47. MacNaughton WK (2000) Review article: new insights into the pathogenesis of radiation-induced intestinal dysfunction. Ailment Pharmacol Ther 14:523–528
48. Donaldson SS, Jundt S, Ricour C et al (1975) Radiation enteritis in children. Cancer 35:1167–1178
49. Sher ME, Bauer J (1990) Radiation induced enteropathy. Am J Gastroenterol 85:121–128
50. Lal DR, Foroutan HR, Su WT et al (2006) The management of treatment-related esophageal compilations in children and adolescents with cancer. J Pediatr Surg 41:495–499
51. Birman C, Beckenham E (1998) Acquired tracheo-esophageal fistula in the pediatric population. Int J Pediatr Otorhinolaryngol 44:109–113
52. Moree JS, Bhakta MG, Ledbetter J (2006) Complication of mediastinal mass: acquired tracheoesophageal fistula associated with t-cell lymphoblastic lymphoma. Pediatr Pulmonol 41:688–689

53. Bouyn CI, Leciere J, Raimondo G et al (2003) Hepatic focal nodular hyperplasia in children previously treated for a solid tumor. Incidence, risk factors, and outcome. Cancer 97:3107–3113
54. Towbin AJ, Luo GG, Yin H, Mo JQ (2011) Focal nodular hyperplasia in children, adolescents, and young adults. Pediatr Radiol 41:341–349
55. Anderson L, Gregg D, Margolis D et al (2010) Focal nodular hyperplasia in pediatric allogeneic hematopoietic cell transplant: case series. Bone Marrow Transplant 45:1357–1359
56. Masetti R, Colecchia A, Rondelli R et al (2013) Benign hepatic nodular lesions after treatment for childhood cancer. J Pediatr Gastroenterol Nutr 56:151–155
57. Pillon M, Carucci NS, Mainardi C et al (2015) Focal nodular hyperplasia of the liver: an emerging complication of hematopoietic SCT in children. Bone Marrow Transplant 50:414–419
58. Chavhan GB, Mann E, Kamath BM, Babyn PS (2014) Gadobenate-dimeglumine-enhanced magnetic resonance imaging for hepatic lesions in children. Pediatr Radiol 44:1266–1274
59. Halonen P, Mattila J, Ruuska T et al (2003) Liver histology after current intensified therapy for childhood acute lymphoblastic leukemia: microvascular fatty change and siderosis are the main findings. Med Pediatr Oncol 40:148–154
60. Ktena YP, Athanasiadou A, Lambrou G et al (2013) Iron chelation with deferasirox for the treatment of secondary hemosiderosis in pediatric oncology patients: a single-center experience. J Pediatr Hematol Oncol 35:447–450
61. Chotsampancharoen T, Gan K, Kasow KA et al (2009) Iron overload in survivors of childhood leukemia after allogeneic hematopoietic stem cell transplantation. Pediatr Transplant 13:348–352

62. Vag T, Kentouche K, Krumbein I et al (2011) Noninvasive measurement of liver iron concentration at MRI in children with acute leukemia: initial results. Pediatr Radiol 41:980–984

63. Hankins JS, McCarville MB, Loeffler RB et al (2009) R2* magnetic resonance imaging of the liver in patients with iron overload. Blood 113:4853–4855

64. McCarville MB, Hillenbrand CM, Loeffler RB et al (2010) Comparison of whole liver and small region-of-interest measurements of MRI liver R2* in children with iron overload. Pediatr Radiol 40:1360–1367

65. Nobili V, Dhawan A (2008) Are children after liver transplantation more prone to non-alcoholic fatty liver disease? Pediatr Transplant 12:611–613

66. Mayson S, Parker V, Schutta M et al (2013) Severe insulin resistance and hypertriglyceridiemia after childhood total body irradiation. Endocr Pract 19:51–58

67. Locasciulli A, Testa M, Valsecchi MG et al (1997) Morbidity and mortality due to liver disease in children undergoing allogenic bone marrow transplantation: a 10 year prospective study. Blood 90:3799–3805

68. Castellino S, Muir A, Shah A et al (2010) Hepato-biliary late effects in survivors of childhood and adolescent cancer: a report from the Children's Oncology Group. Pediatr Blood Cancer 54:663–669

69. Barnard JA, Marshall GS, Neblett WW et al (1986) Noncirrhotic portal fibrosis after Wilms' tumor therapy. Gastroenterology 90:1054–1056

70. Maturen KE, Fent MU, Wasnick AP et al (2013) Imaging effects of radiation therapy in the abdomen and pelvis: evaluating 'innocent bystander' tissues. Radiographics 33:599–619

71. Bianchetti MG, Kanaka C, Ridolfi-Luthy A et al (1991) Persisting renotubular sequelae after cisplatin in children and adolescents. Am J Nephrol 11:127–130

72. McCune JS, Friedman DL, Schuetze S et al (2004) Influence of age upon ifosfamide-induced nephrotoxicity. Pediatr Blood Cancer 42:427–432
73. Cassady JR (1995) Clinical radiation nephropathy. Int J Radiat Oncol Biol Phys 31:1249–1256
74. Wong-You-Cheong JJ, Woodward PJ, Manning MA, Davis CJ (2006) From the archives of the AFIP: inflammatory and nonneoplastic bladder masses: radiologic-pathologic correlation. Radiographics 26:1847–1868
75. Smith WA, Li C, Nottage KA et al (2014) Lifestyle and metabolic syndrome in adult survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study. Cancer 120:2742–2750
76. Chemaitilly W, Li Z, Huang S et al (2015) Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the St. Jude Lifetime Cohort study. J Clin Oncol 33:492–500
77. Cowles RA, Gewanter RM, Kandel JJ (2007) Ovarian repositioning in pediatric cancer patients: flexible techniques accommodate pelvic radiation fields. Pediatr Blood Cancer 49:339–341
78. Gawade PL, Hudson MM, Kaste SC et al (2014) A systematic review of selected musculoskeletal late effects in survivors of childhood cancer. Curr Pediatr Rev 10:249–262
79. Lockney NA, Friedman DN, Wexler LH et al (2016) Late toxicities of intensity-modulated radiation therapy for head and neck rhabdomyosarcoma. Pediatr Blood Cancer 63:1608–1614
80. Pacheco R, Stock H (2013) Effects of radiation on bone. Curr Osteoporos Rep 11:299–304
81. Bluemke DA, Fishman EK, Scott WW (1994) Skeletal complications of radiation

therapy. Radiographics 14:111–121

82. Polgreen LE, Petryk A, Dietz AC et al (2012) Modifiable risk factors associated with bone deficits in childhood cancer survivors. BMC Pediatr 12:40
83. den Hoed MAH, Klap BC, teWinkel ML et al (2015) Bone mineral density after childhood cancer in 346 long-term adult survivors of childhood cancer. Osteoporos Int 26:521–529
84. Fletcher BD (1997) Effects of pediatric cancer therapy on the musculoskeletal system. Pediatr Radiol 27:623–636
85. Fletcher BD, Crom DB, Krance RA, Kun LE (1994) Radiation-induced bone abnormalities after bone marrow transplantation for childhood leukemia. Radiology 191:231–235
86. Roebuck DJ (1999) Skeletal complications in pediatric oncology patients. Radiographics 19:873–885
87. Smith J (1982) Radiation-induced sarcoma of bone: clinical and radiographic findings in 43 patients treated for soft-tissue neoplasms. Clin Radiol 33:205–221
88. Schwartz AM, Leonidas JC (1984) Methotrexate osteopathy. Skeletal Radiol 11: 13–16
89. Price AP, Abramson SJ, Hwang S et al (2011) Skeletal imaging effects of pamidronate therapy in osteosarcoma patients. Pediatr Radiol 41:451–458

Legends

Fig. 1 Chronic graft-versus-host disease (GVHD) with liver involvement in a 7-year-old boy post hematopoietic stem cell transplantation for acute lymphoblastic leukemia. **a, b** Axial T2-W MR images of the liver demonstrate increased periportal signal (**a**, *arrows*) and dilatation of extrahepatic bile duct (**b**, *arrowhead*). **c** High-resolution US image of the porta hepatis

demonstrates common bile duct (*arrowhead*) with wall thickening and luminal dilatation *(calipers*). Findings of increased periportal signal, duct dilatation and duct wall thickening seen in this child with biopsy-proven chronic GVHD resemble those seen in primary sclerosing cholangitis

Fig. 2 Second malignant neoplasm. Osteosarcoma of the right iliac crest in a 14-year-old girl, 9 years post radiotherapy for treatment of a pelvic rhabdomyosarcoma. **a** Anteroposterior pelvic radiograph reveals increased bony sclerosis and periosteal reaction on the medial aspect of the right iliac bone (*arrow*). **b, c** MRI. Coronal short tau inversion recovery (**b**) and axial T1-W fat-saturated post-contrast (**c**) images demonstrate a large, heterogeneously enhancing soft-tissue lesion within the area of concern (*arrows*)

Fig. 3 Thyroid complications. Thyroid nodules after radiation treatment for a nasopharyngeal rhabdomyosarcoma in a 10-year-old girl. Color Doppler US image of the right lobe of the thyroid gland 4 years after therapy demonstrates a thyroid nodule with hypoechoic halo (*arrow*), favored as benign in origin

Fig. 4 Pulmonary sequelae. Pulmonary fibrosis in a 14-year-old girl who 6 years prior had resection and radiation treatment for thoracic left paraspinal sarcoma. Axial (**a**) and coronal (**b**) CT images of the lung demonstrate areas of fibrosis, traction bronchiectasis and volume loss in the superior segment of the left upper lobe (*arrows*), which was in the radiation field

Fig. 5 Cardiomyopathy. Dilated cardiomyopathy in a 15-year-old girl with history of acute myeloid leukemia and treatment with anthracycline. Anteroposterior radiograph of the chest demonstrates moderate to marked cardiomegaly. A left ventricular assist device (*arrow*) has been placed to treat the cardiac dysfunction. A mediastinal pigtail drainage catheter, right central venous line and nasogastric tubes are seen

Fig. 6 Radiation enteropathy in a 7-year-old girl with a history of ruptured pelvic rhabdomyosarcoma necessitating embolization, radiotherapy and intestinal diversion and

formation of loop ileostomy within the right upper quadrant 1.5 years earlier. Anteroposterior projection of the pelvis obtained during a fluoroscopic loopogram via the distal ileostomy stoma demonstrates narrowing and poor distension of the distal transverse, descending and sigmoid colon, and rectum. Note the embolization coils within the right lower quadrant (*arrow*) and presence of calcified gallstones in the right upper quadrant. There is diffuse demineralization and coarse trabeculation of the visualized bones

Fig. 7 Radiation esophagitis resulting in esophageal narrowing and stricture formation in a 16-year-old boy who had been treated with mediastinal radiation and five cycles of chemotherapy at age 8 years for Hodgkin lymphoma. Lateral projection of a water-soluble contrast esophagram demonstrates long-segment smooth stricture in the mid-thoracic esophagus (*arrow*)

Fig. 8 Hepatic complications. Focal nodular hyperplasia in a 5-year-old boy who was previously treated with chemotherapy and bone marrow transplantation for neuroblastoma. **a, b** Axial MRI. The liver lesions (*arrows*) are slightly bright on T2-weighted image (**a**) and remain iso- to hyperintense to liver parenchyma on the hepatobiliary phase 45 min post gadobenate contrast administration (**b**)

Fig. 9 Iron deposition in a 12-year-old boy with disseminated pineoblastoma and hepatic metastases (*arrows*) as seen on (**a**) out-phase short echo time (TE) MRI and (**b**) in-phase long TE MRI. Compared to the out-phase image with short TE (**a**) the liver and spleen lose signal on in-phase MR image with longer TE (**b**), suggestive of siderosis

Fig. 10 Marked renal atrophy in a 10-year-old boy was diagnosed at 2 years of age with right adrenal neuroblastoma and was treated with surgery, chemotherapy and radiotherapy. **a** Coronal reformatted post-intravenous-contrast CT image demonstrates a small right kidney (*arrow*) with cortical thinning and loss of parenchymal volume. The kidney was normal at the

time of tumor diagnosis. **b** Nuclear medicine study, posterior projection, to assess the boy's glomerular filtration rate demonstrates total loss of function in the right kidney (*arrow*)

Fig. 11 Gonadal dysfunction. Ovarian transposition in a teenage girl treated with radiotherapy for pelvic Hodgkin lymphoma. **a** Axial post-intravenous-contrast CT image demonstrates left pelvic lymphadenopathy (*arrowheads*), right ovary (*arrow*) and left ovary (*dashed arrow*). **b** Axial post-intravenous-contrast CT image after the ovarian transposition demonstrates left ovary now placed on the right side (*dashed arrow and outlined by blue line*) to prevent radiation exposure. **c** Axial non-contrast CT image shows radiotherapy planning. The thick red line outlines the target volume and the thin lines are doses of 5 Gy (*purple*), 15 Gy (*teal*) and 25 Gy (*yellow*)

Fig. 12 Scoliosis in a 12-year-old girl with recurrent mesoblastic nephroma and treatment with surgery and radiation. **a** Axial CT image of the abdomen on day 2 of age demonstrates a large heterogeneously enhancing right renal mass (*arrowheads*). **b** Posteroanterior radiograph of the spine at the age of 12 years shows levoconvex scoliosis of the lumbar spine (*arrow*)

Fig. 13 Pelvic hemiatrophy in a 19-year-old man with history of right femoral Ewing sarcoma treated with surgery and radiation at the age of 7 years. Pelvic radiograph demonstrates a significantly smaller iliac bone compared to the normal left side. The man had undergone a limb-sparing procedure of the right femur with placement of bone graft and orthopedic hardware (*arrows*) in the visualized right upper thigh, replacing the femur

Fig. 14 Slipped capital femoral epiphysis in a 12-year-old girl with history of radiation for left pelvic rhabdomyosarcoma 7 years prior. Anteroposterior (**a**) and frog-leg (**b**) projections of the pelvis show left slipped capital femoral epiphysis, with some deformity of the epiphysis (*arrows*). Note also the atrophy of left pelvic bone

Fig. 15 Compression fractures in a 30-year-old man with a history of acute lymphoblastic leukemia treatment. Lateral CT scout image of the spine shows multilevel vertebral

compression fractures and endplate depression with decrease in bone mineral density. His bone mineral density Z-score by quantitative computed tomography (QCT) was –1.91

Fig. 16 Radiation osteitis in a 14-year-old boywho had previous radiotherapy for Ewing sarcoma centered within the right inferior pubic ramus bone (*arrows*). **a, b** Anteroposterior pelvic radiographs taken during the primary diagnosis at 8 years of age (**a**) and at age of 14 years (**b**) demonstrate progressive right iliac atrophy, heterogeneous sclerosis at the right acetabulum, shortened right femoral neck and loss of height of the right proximal femoral epiphysis. **c** Coronal CT with bone windows obtained at age 13 years better demonstrates the bony changes in the right acetabulum and proximal femur (*arrow*)

Fig. 17 A small osteochondroma in an 8-year-old girl previously treated with craniospinal irradiation for medulloblastoma. **a** Axial CT with soft-tissue windows demonstrates a small osseous lesion (*arrow*) extending into the spinal canal at the T7–8 level, with mass effect on the thecal sac, although not causing any spinal cord compression. **b** T1-W fat-saturated post-contrast axial MR image at the same vertebral level reveals rim enhancement of the lesion (*arrow*) in keeping with the cartilaginous cap of the osteochondroma

Fig. 18 A distal femoral osteochondroma in a 12-year-old boy 7 years post radiotherapy for stage IV neuroblastoma. Anteroposterior (**a**) and lateral (**b**) radiographs of the right knee demonstrate a small osteochondroma on the posterior medial aspect of the distal femur (*arrows*). There are coarse bony trabeculations of the metaphyses with underlying demineralization

Table 1 Late non-neurological complications of cancer therapy in children by organ system	
Organ system	**Late effects of treatment**
Multisystem	Chronic graft-versus-host disease (GVHD) commonly mimicking sclerosing cholangitis; bronchiolitis obliterans (associated with allogeneic hematopoietic stem cell transplant [HSCT]) Second malignant neoplasms — breast, thyroid, brain and bone tumors (associated with radiation therapy), acute myeloid leukemia and myelodysplasia (associated with chemotherapy)
Endocrine	**Thyroid** Hypothyroidism, thyroid nodules, hyperthyroidism, thyroid carcinoma (commonly associated with radiotherapy or HSCT) **Gonads** Azoospermia, delayed puberty, absence of secondary sex characteristic development, decreased fertility, infertility (can be caused by pelvic radiotherapy or exposure to alkylating agents) **Pituitary** Decreased growth hormone, panhypopituitarism (seen with total body irradiation)
Pulmonary	Reduced pulmonary function, radiation pneumonitis, pulmonary fibrosis, interstitial pneumonitis, restrictive/obstructive lung disease, recurrent pneumonia, pleurisy, thymic cysts, bronchiolitis obliterans organizing pneumonia (BOOP) Pulmonary features, particularly pulmonary fibrosis, are most commonly associated with chemotherapy (bleomycin, busulfan, CCNU, BCNU, cyclophosphamide) and radiation therapy
Cardiac	Cardiomyopathy, congestive cardiac failure (high association with anthracycline chemotherapy), pericarditis (high association with chest irradiation), valvular heart disease, coronary arterial disease, premature atherosclerosis, impaired myocardial growth

Gastrointestinal	**Enteric** Chronic radiation enteropathy, mucosal ulceration, stricture formation, malabsorption, tracheoesophageal fistulas (associated with radiotherapy or chemotherapy) and bowel obstruction/ileus, volvulus, intussusception, adhesions (associated with prior surgical intervention) **Hepatic** Focal nodular hyperplasia, hemochromatosis (from multiple blood transfusions), hepatosteatosis, hepatic fibrosis, hepatic cirrhosis. All features can be associated with prior radiotherapy, chemotherapy or HSCT
Urinary	Bladder fibrosis, radiation-induced nephropathy, renal atrophy, end-stage renal disease, enterocystic fistulae, acute tubular dysfunction with increased excretion of electrolytes, hypophosphatemic rickets (from chemotherapy or radiotherapy)
Musculoskeletal	Leg-length discrepancy, soft-tissue hypoplasia, slipped capital femoral epiphyses, pathological fractures from reduced bone mineral density, radiation osteitis, short stature, scoliosis, osteochondroma formation, poor dental enamel and root formation (associated with radiation therapy, or chemotherapy with methotrexate and corticosteroids)

BCNU bis-chloroethylnitrosourea
CCNU 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea

Figure 1a

Click here to download Figure Figure 1a. GVHD on Liver Bx 7yb ALL post bmt 2 ax t2.tif

Figure 1b

Click here to download Figure Figure 1b. GVHD on Liver Bx 7yb ALL post bmt 4 ax t2.tif

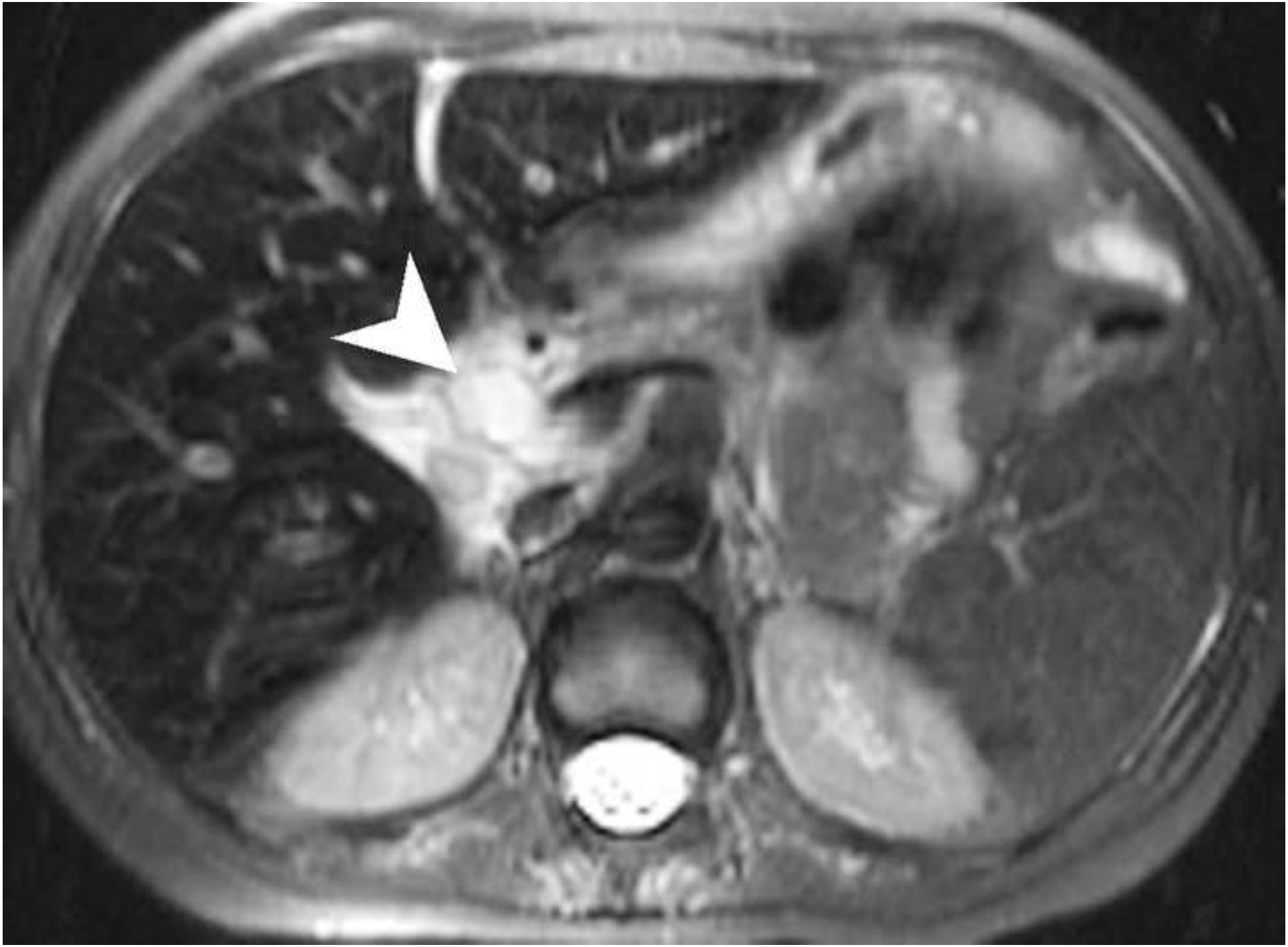

Figure 1c

Click here to download Figure Figure 1c. GVHD on Liver Bx 7yb ALL post bmt 6 us cbd thick.tif

Figure 2a

Click here to download Figure Figure 2a.tif

Figure 2b

Click here to download Figure Figure 2b.tif

Figure 2c

Click here to download Figure Figure 2c.tif

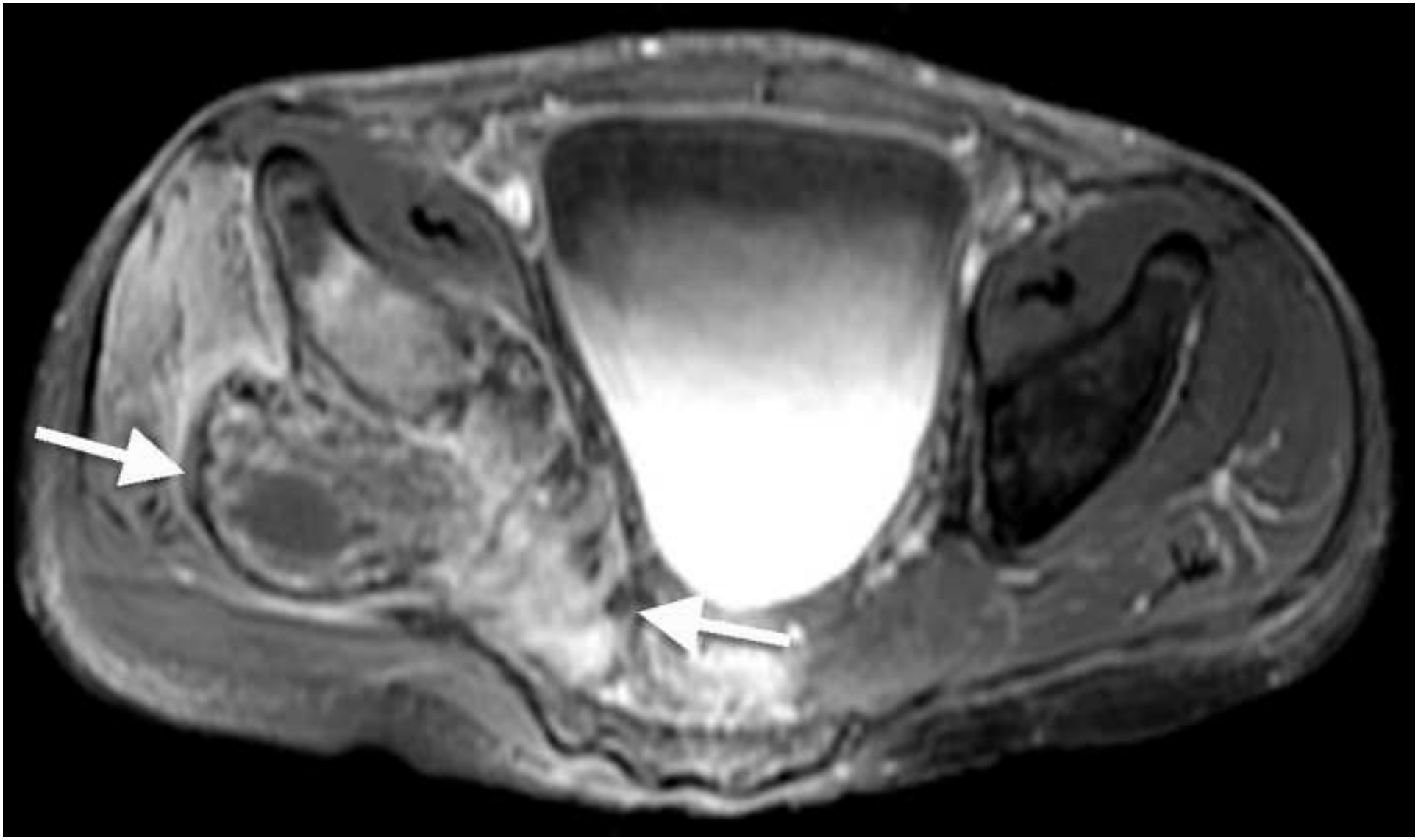

Figure 3

Click here to download Figure Figure 3.tif

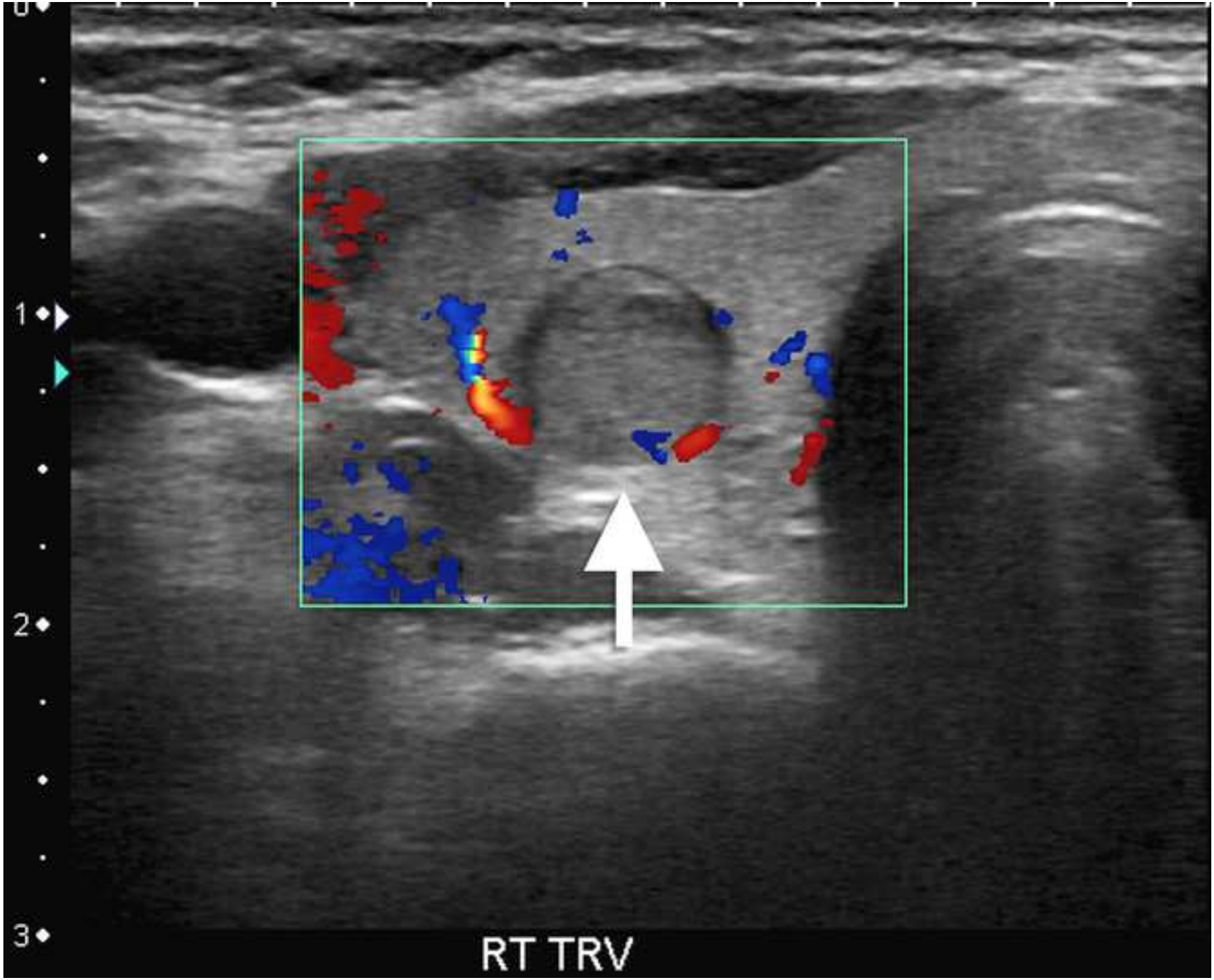

Figure 4a

Click here to download Figure Figure 4a. Recall puemonits 14yG paraspinal sarcoma resected local Radiation 6 yrs ago 3.tif

Figure 4b

Click here to download Figure Figure 4b. Recall puemonits 14yG paraspinal sarcoma resected local Radiation 6 yrs ago 6.tif

Figure 5

Click here to download Figure Figure 5. Cardiomyopathy dilated Antracycline AML 15g 3 xrc with LVAD.TIF

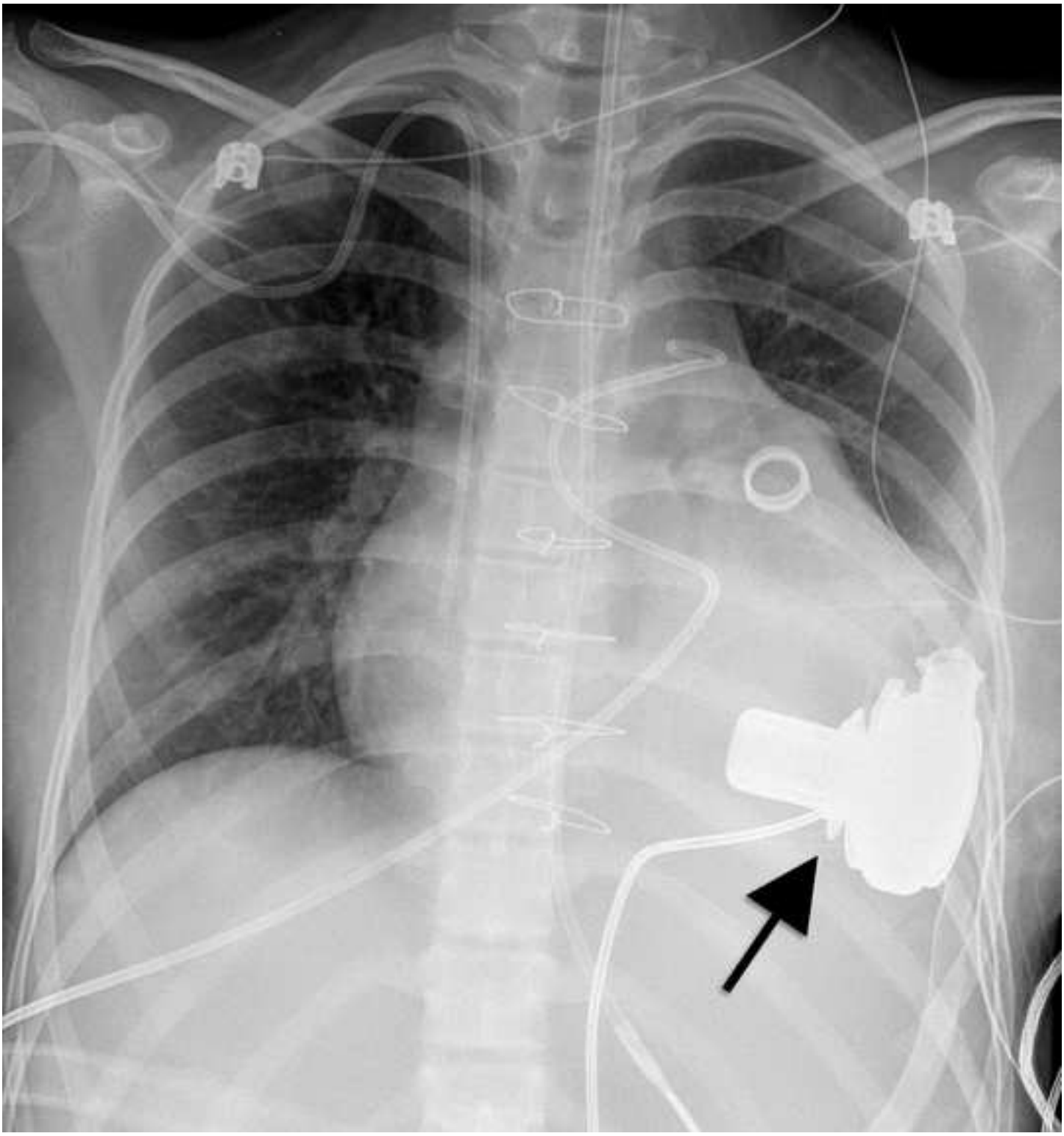

Figure 6

Click here to download Figure Figure 6.tif

Figure 7

Click here to download Figure Figure 7.tif

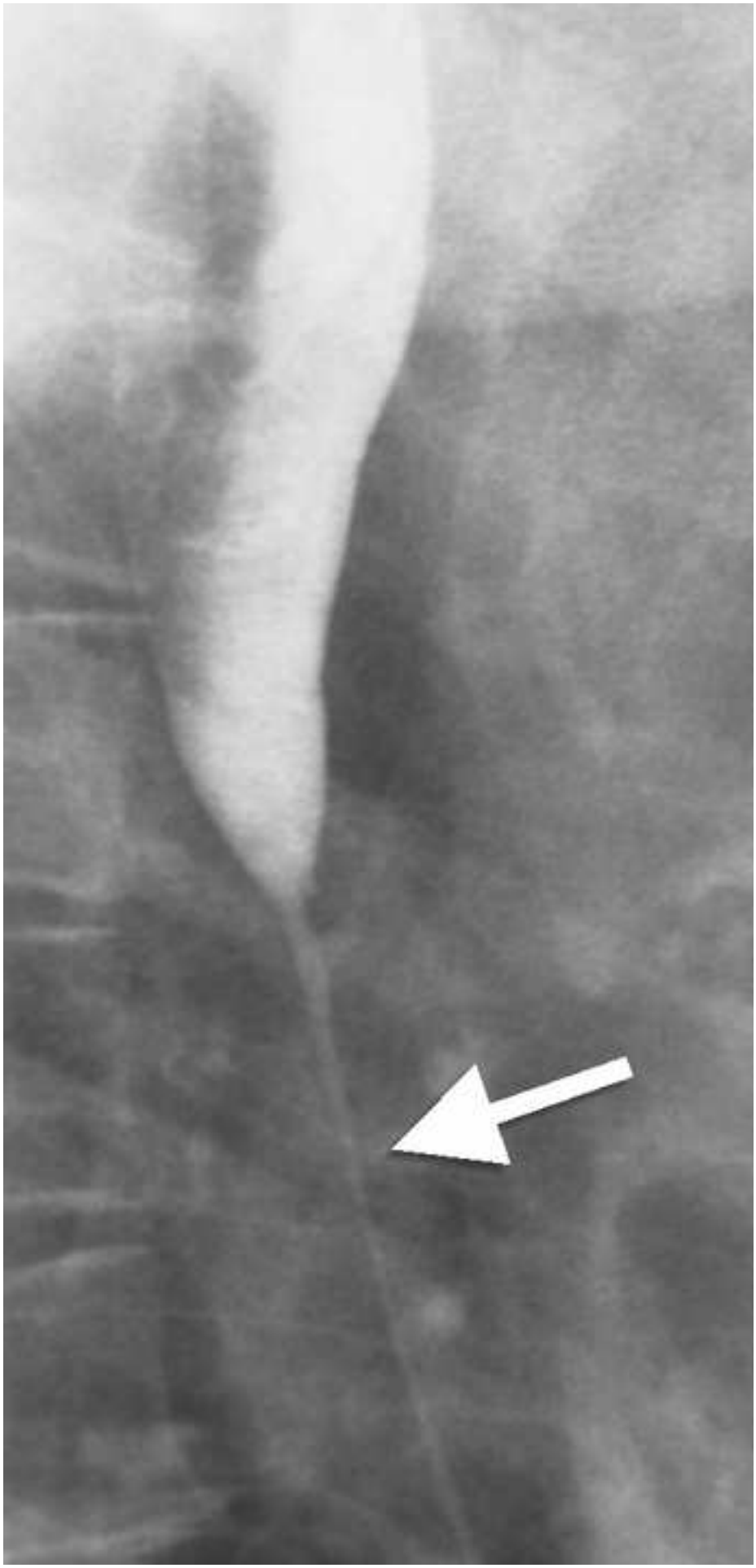

Figure 8a

Click here to download Figure Figure 8a. FNH 4yG sIV NB 1 t2.tif

Figure 8b

Click here to download Figure Figure 8b. FNH 4yG sIV NB 2 45min mH.tif

Figure 9a

Click here to download Figure Figure 9a. Iron overload 12yB dissem Pinealoblastoma high dose CTRT 2 out phase.tif

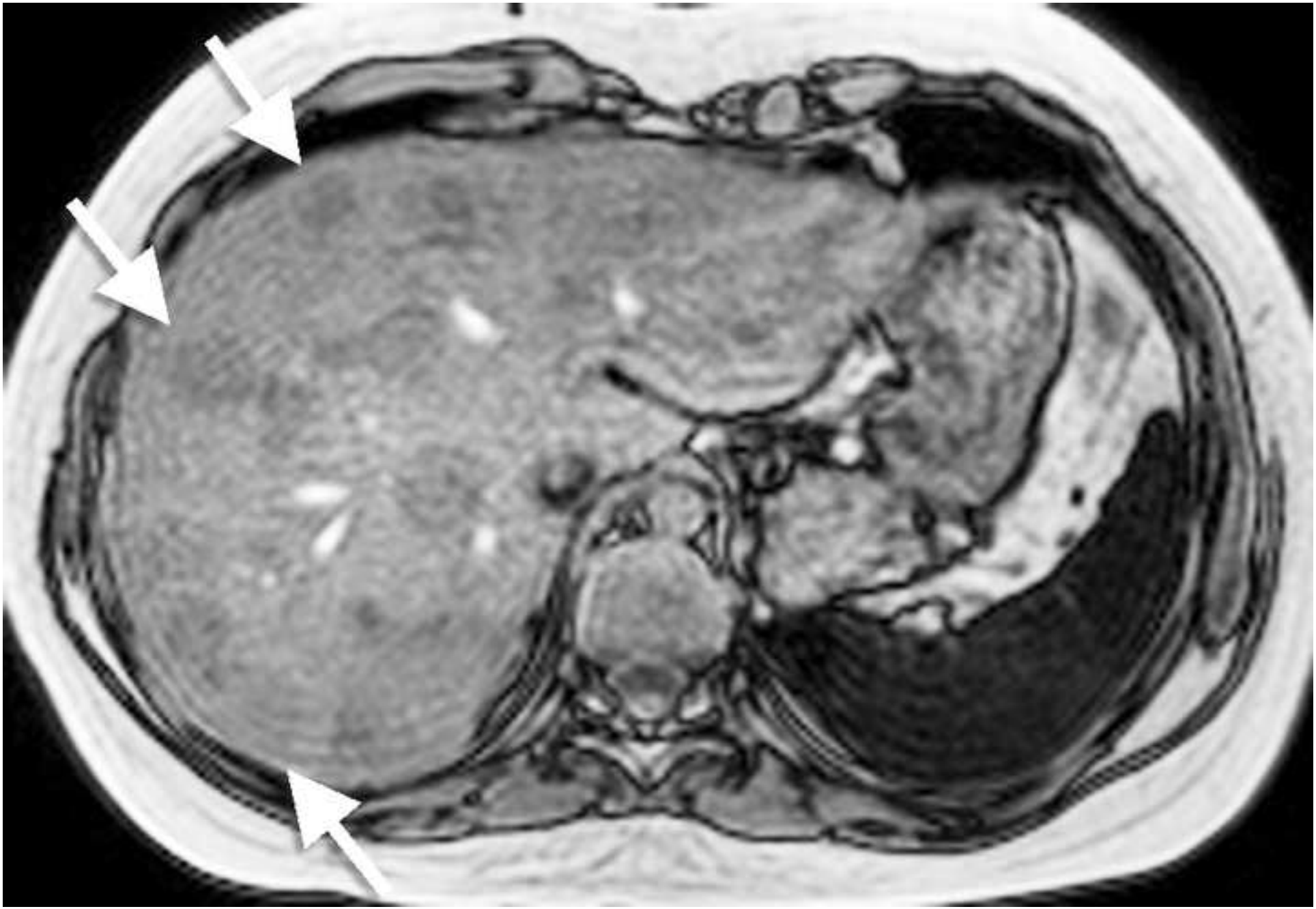

Figure 9b

Click here to download Figure Figure 9b. Iron overload 12yB dissem Pinealoblastoma high dose CTRT 1 in phase.tif

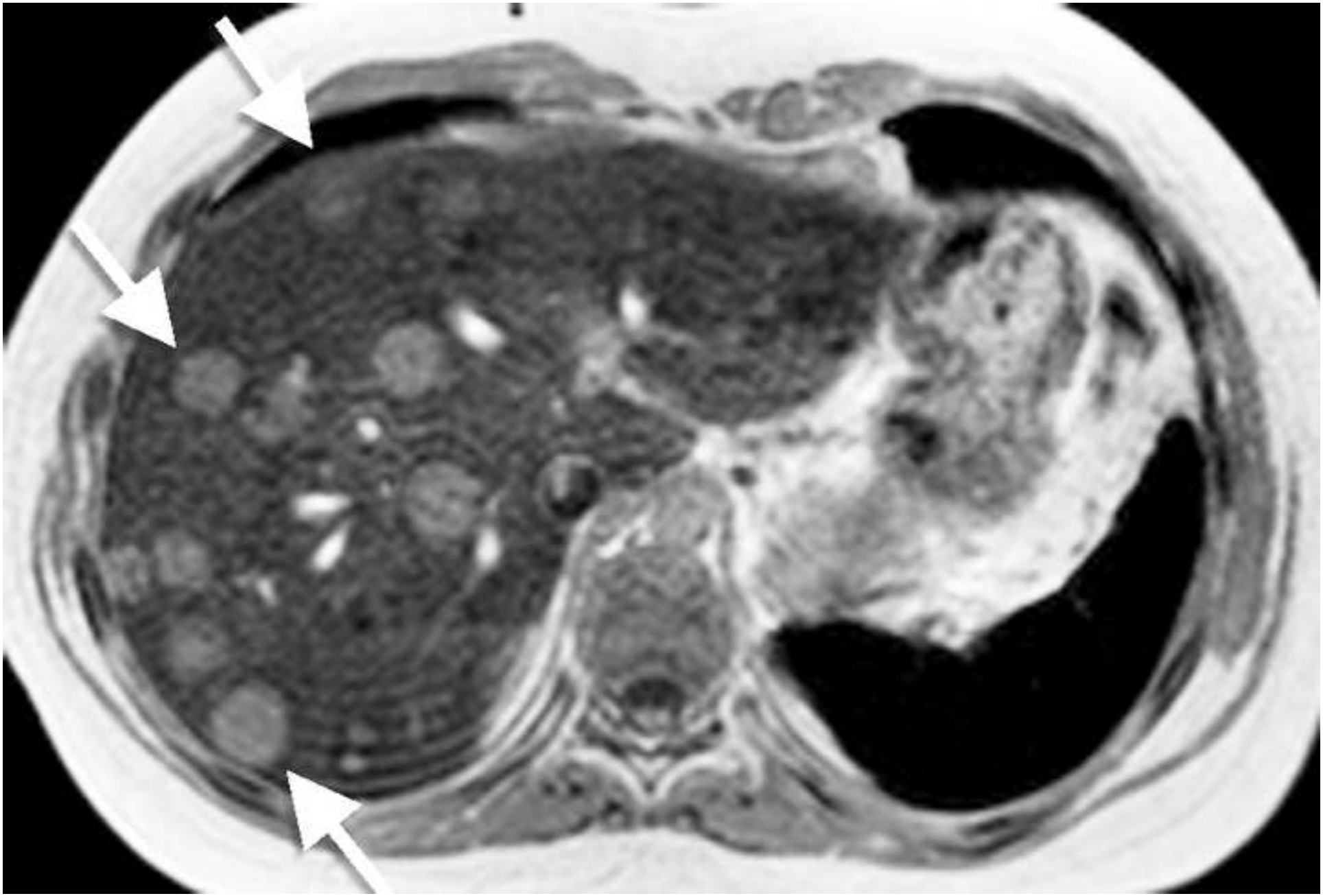

Figure 10a

Click here to download Figure Figure 10a.tif

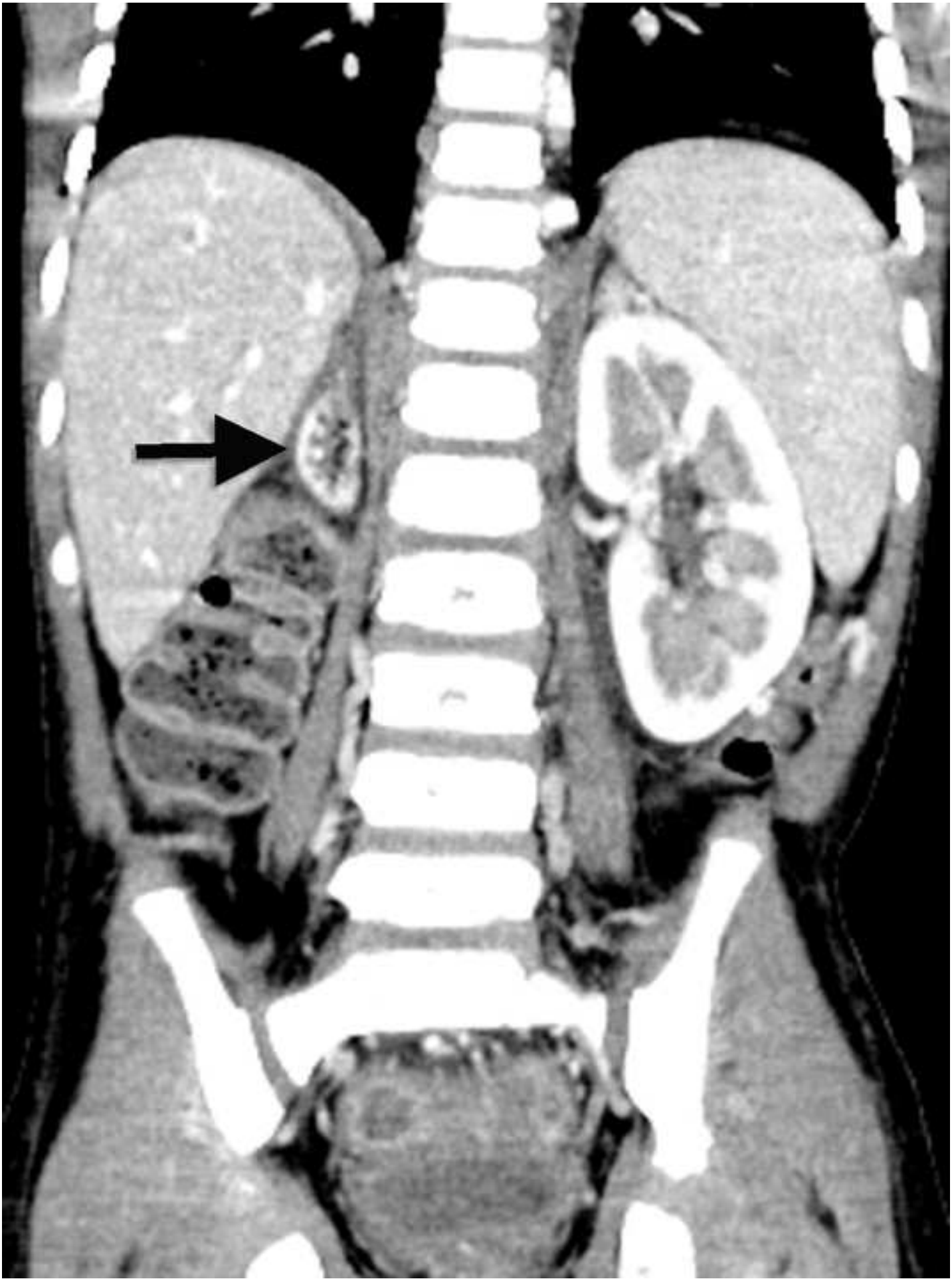

Figure 10b

Click here to download Figure Figure 10b.tif

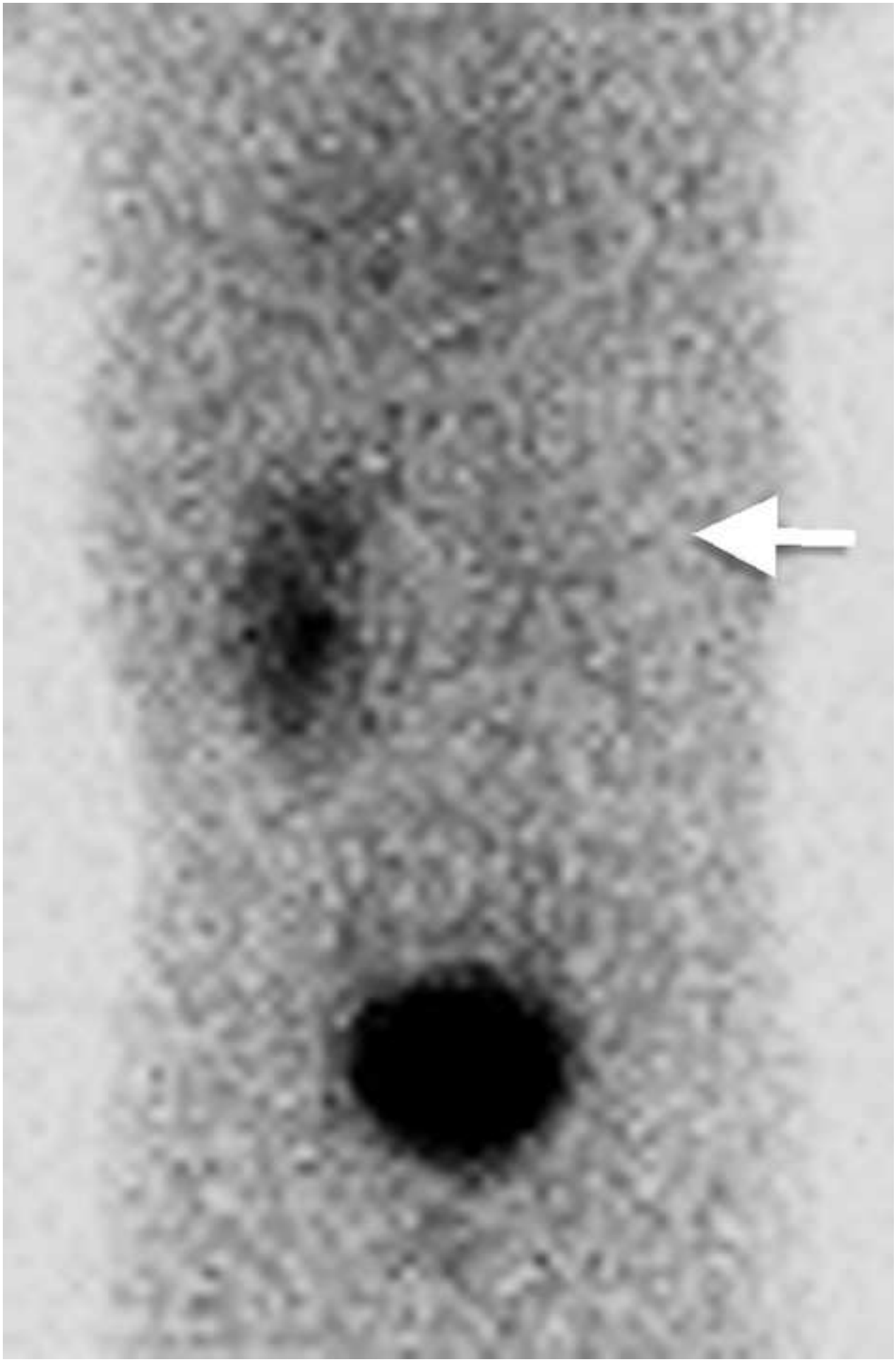

Figure 11a

Click here to download Figure Figure 11a. pre transposition (1).tif

Figure 11b

Click here to download Figure Figure 11b. post transposition (1).tif

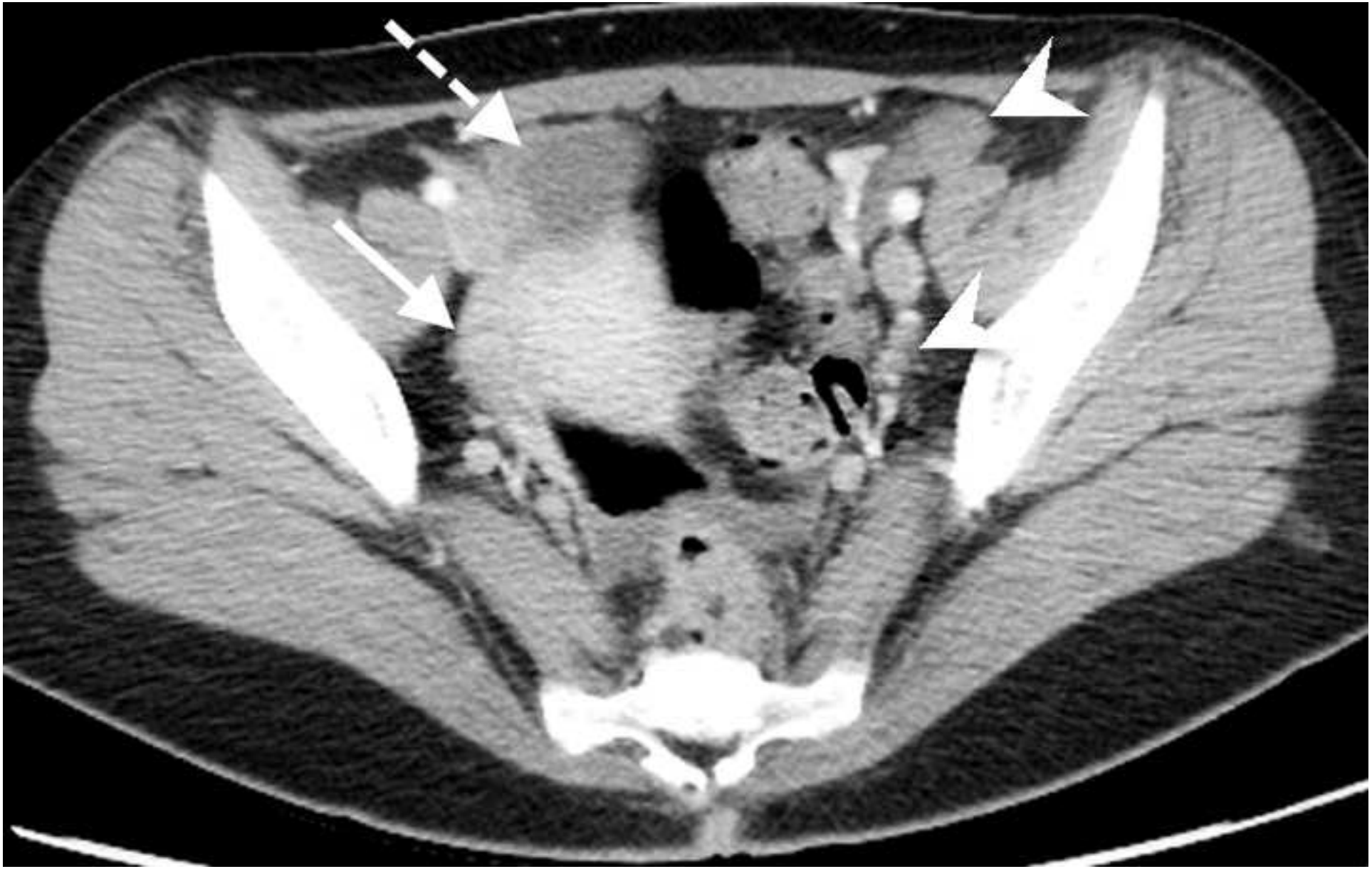

Figure 11c

Click here to download Figure Figure 11c. Ovary_CT (1).TIF

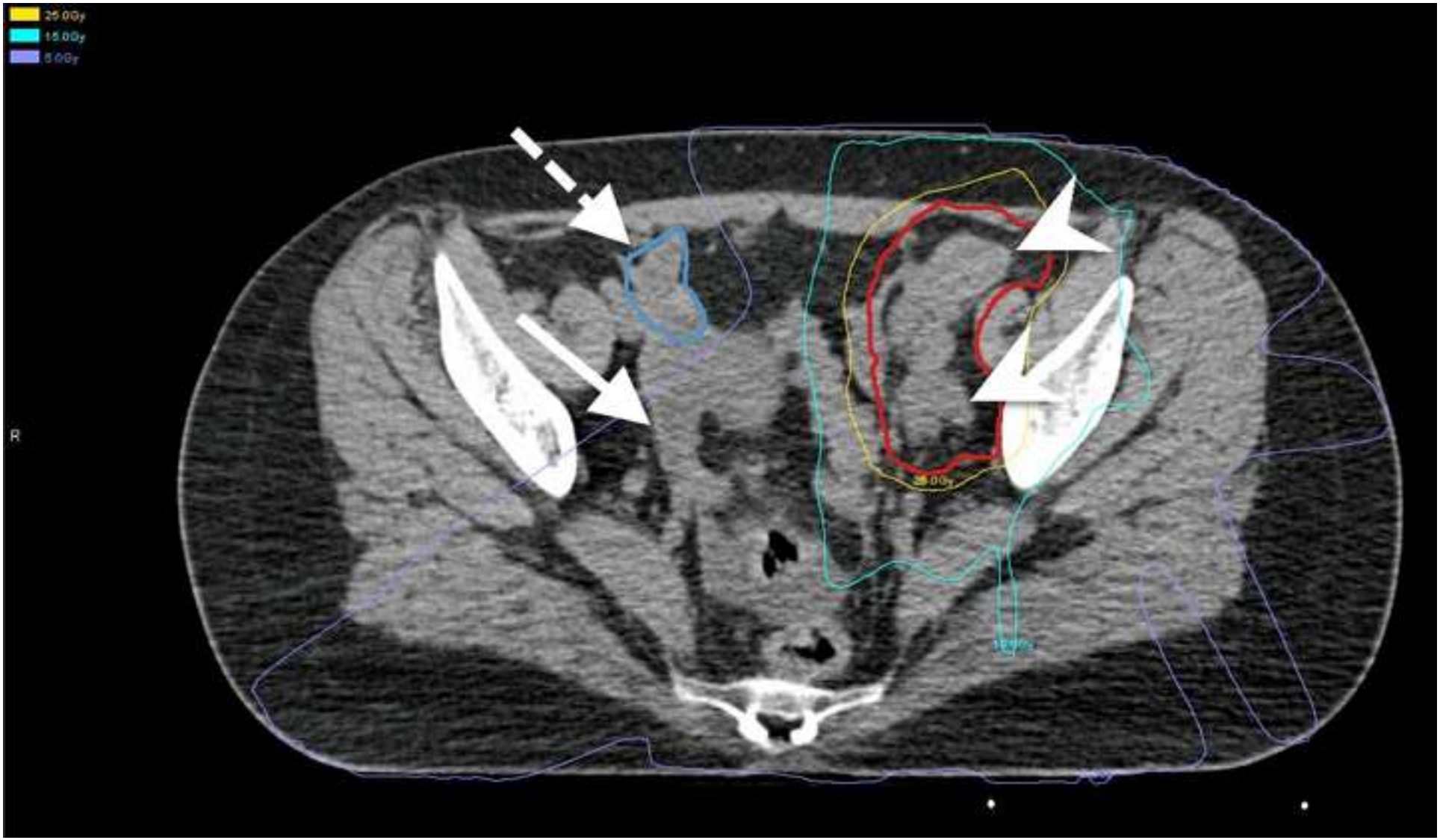

Figure 12a

Click here to download Figure Figure 12a. Socliosis post RadT for recurrent mesobls nephroma rt 1 ct on day 2 rt tumor.tif

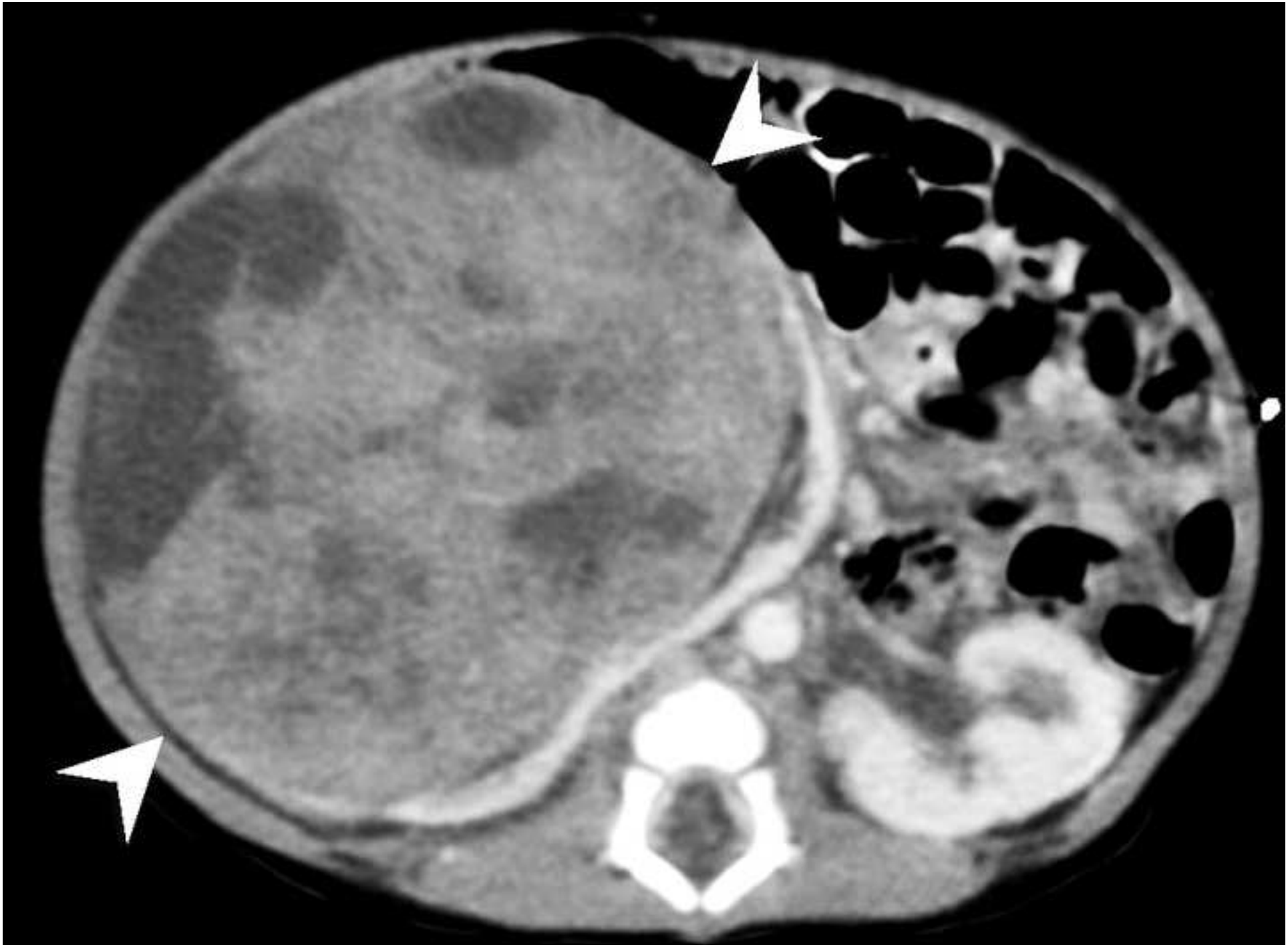

Figure 12b

Click here to download Figure Figure 12b. Socliosis post RadT for recurrent mesobls nephroma rt 3 xr at 12y.tif

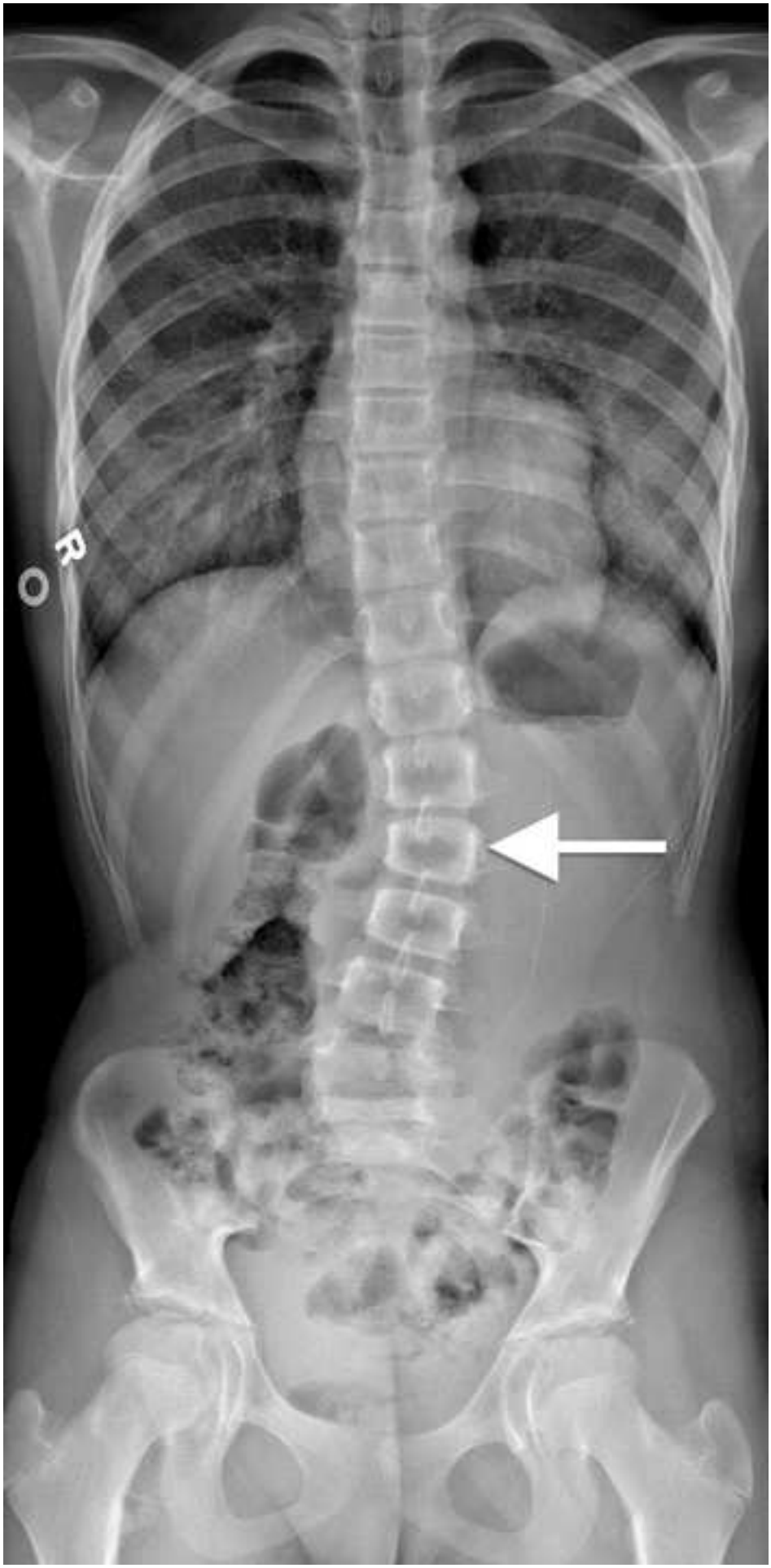

Figure 13

Click here to download Figure Figure 13. Radiation for femoral Ewings 19y 1.tif

Figure 14a

Click here to download Figure Figure 14a. SCFE hypoplasia of hemipelvis 12g RMS left pelvis 7y ago 1.tif

Figure 14b

Click here to download Figure Figure 14b. SCFE hypoplasia of hemipelvis 12g RMS left pelvis 7y ago 2.tif

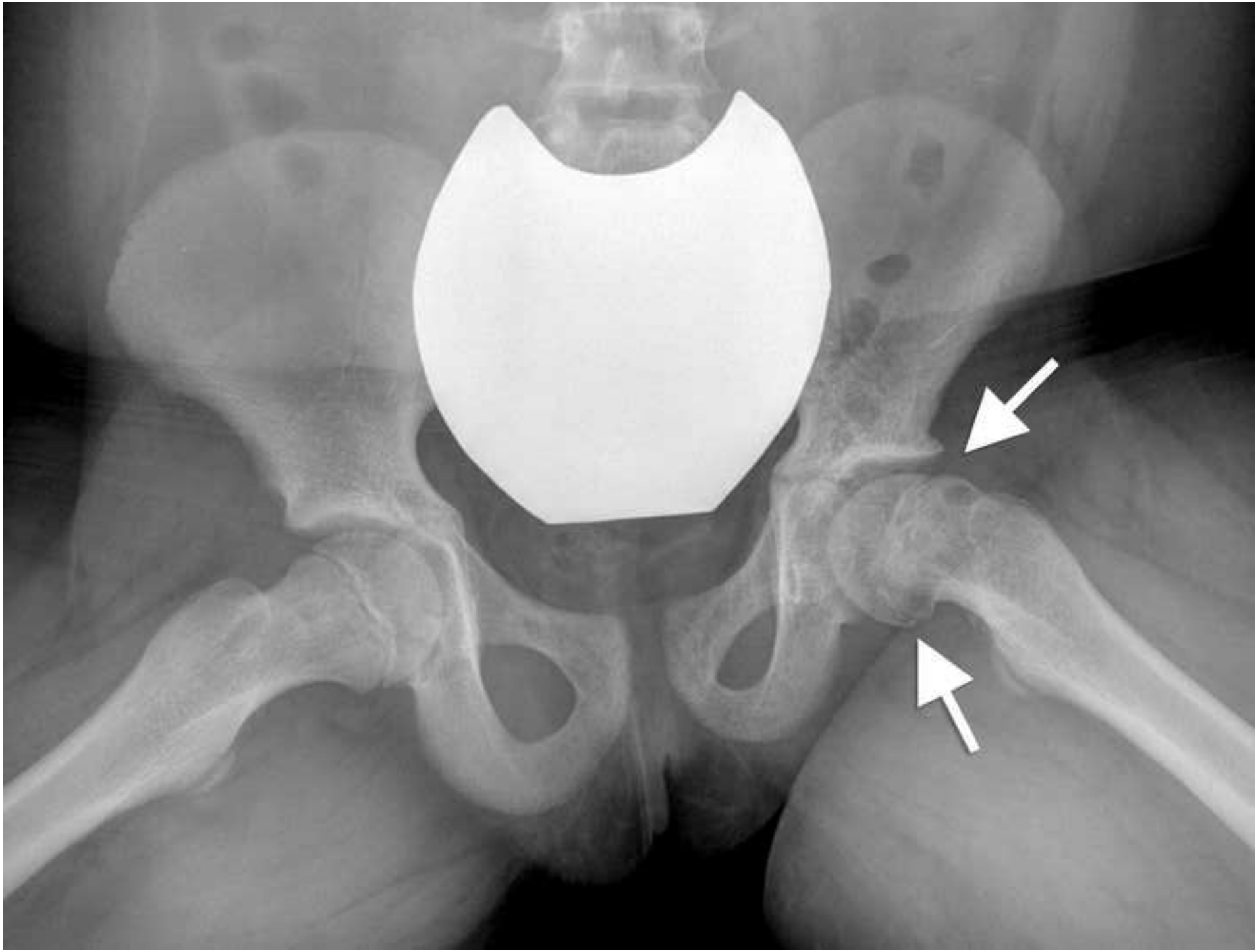

Figure 15

Click here to download Figure Figure 15. mult comp fxs 30yM ALL survivor Z-score-1.91 by Qct.tif

Figure 16a

Click here to download Figure Figure 16a.tif

Figure 16b

Click here to download Figure Figure 16b.tif

Figure 16c

Click here to download Figure Figure 16c.tif

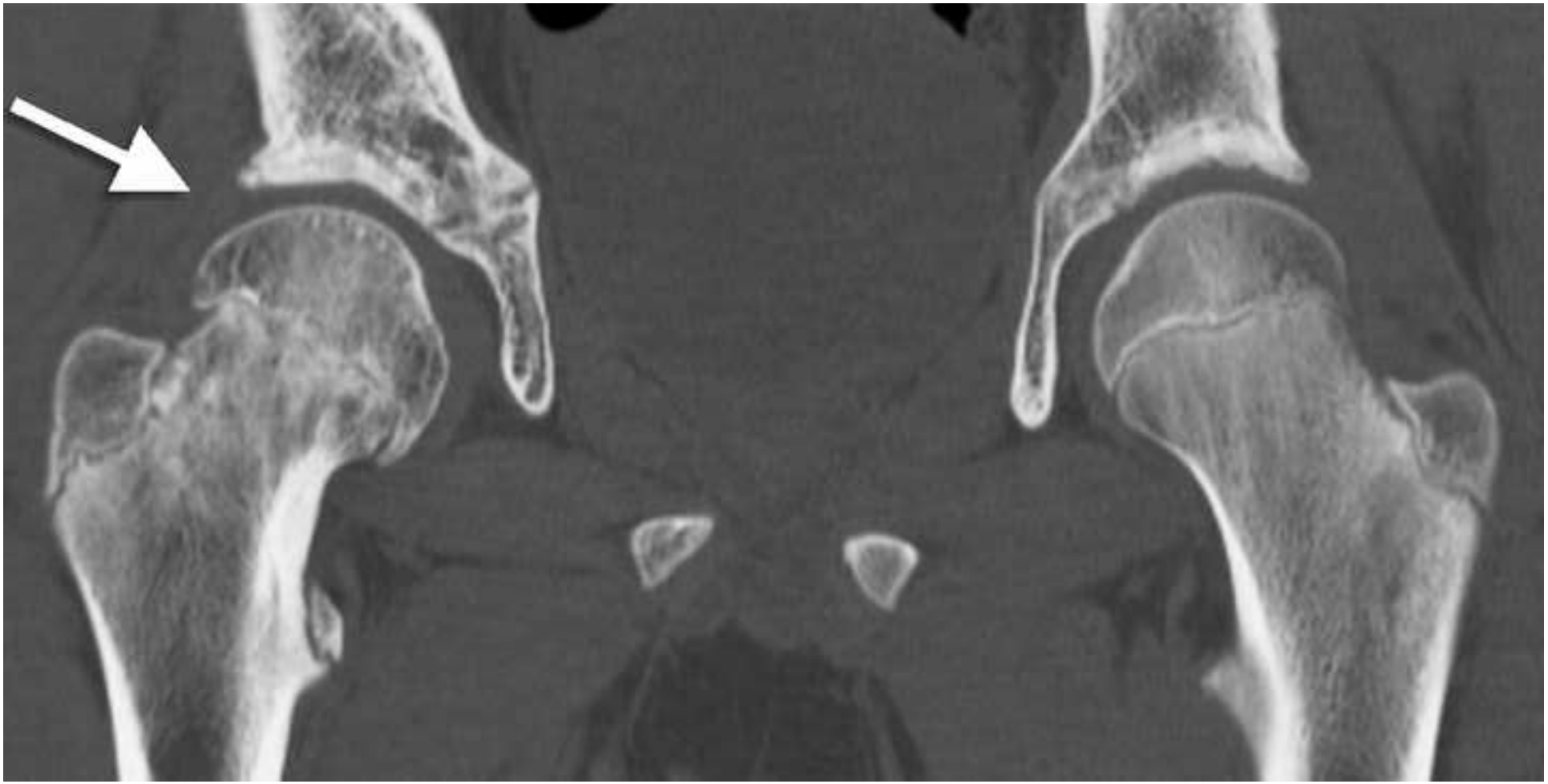

Figure 17a

Click here to download Figure Figure 17a.tif

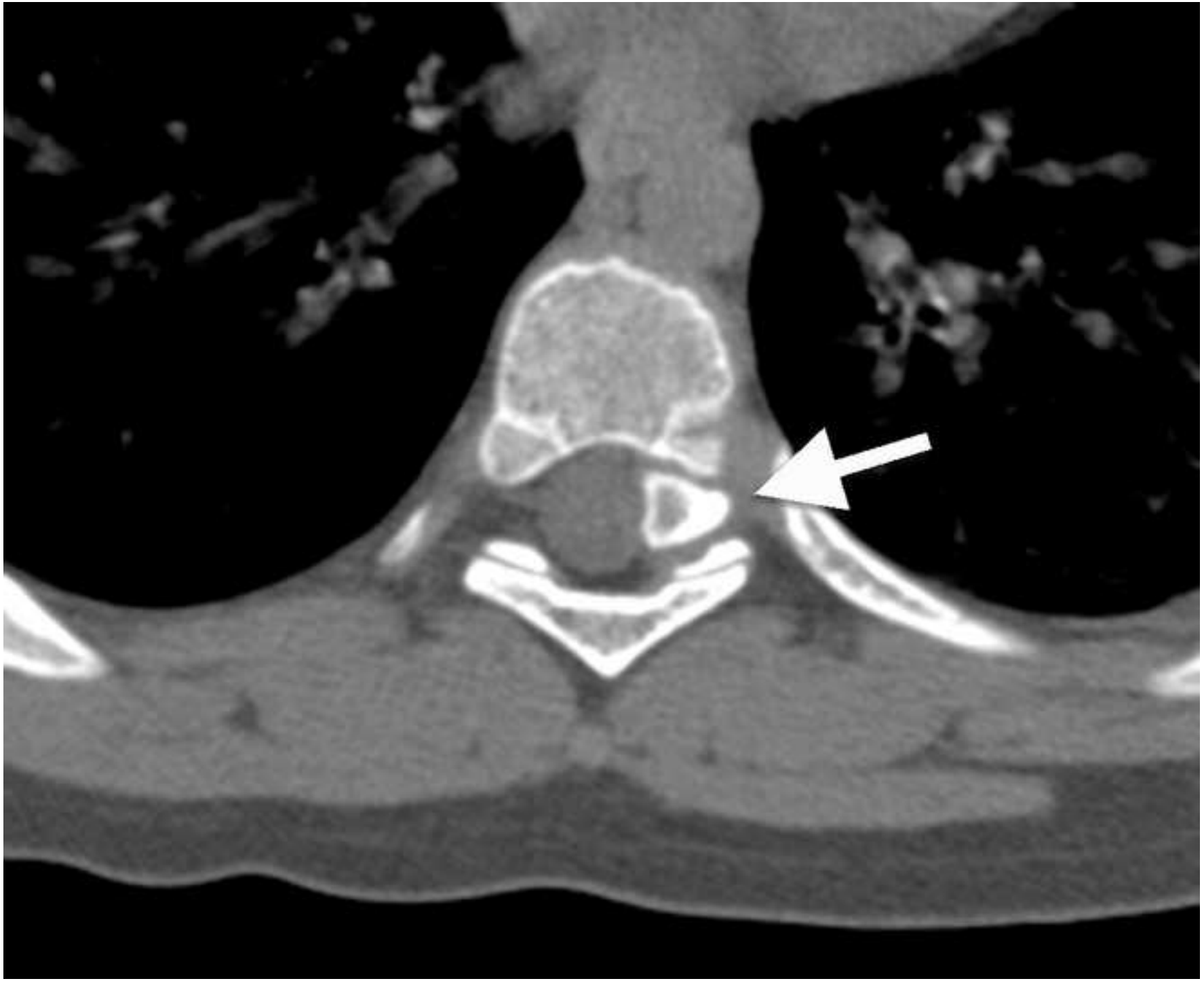

Figure 17b

Click here to download Figure Figure 17b.tif

Figure 18a

Click here to download Figure Figure 18a.tif

Figure 18b

Click here to download Figure Figure 18b.tif

Click here to access/download
Conflict of Interest Form
COI_Chavhan Shelmerdine Nathan.pdf

Click here to access/download
Conflict of Interest Form
COI_Babyn.pdf

Click here to access/download
Conflict of Interest Form
COI_Kaste.pdf

Author's Response to Reviewers' Comments

Click here to download Author's Response to Reviewers' Comments Cover letter 16_00221 R1.docx

Editors' comments:

Ed- 1. The reviewers have provided some comments regarding the illustrations and other entities that might be included to strengthen the presentation. Please consider these carefully. An illustration or illustrations of chronic pulmonary complications seems conspicuously absent and should be added.

Response: Illustrations of pulmonary fibrosis and cardiomyopathy are now added in the manuscript.

Ed- 2. The discussion of bone growth deformity should be expanded with additional illustration(s) and with particular focus on the spine, the pelvis/hips and on the face. I am not sure that I understand the scoliosis case illustrated. The treated tumor was on the right and one would expect the abnormality (undergrowth, fusion) to be on the right not the left – this would cause a levoconvex not a dextroconvex curve. Growth disturbance can be particularly problematic for the hips (small acetabulum) and face (dysmorphism). Should these be discussed more? It would be great to include a slipped capital femoral epiphysis in a post-pelvic radiation patient – they are predisposed at younger age.

Response: Discussion on bone growth disturbances is expanded and imaging examples of major abnormalities have been added. The scoliosis case has been replaced with a new case showing convexity of the curve opposite to the side of tumor.

Ed- 3. If you are unable to find these entities at your own institutions, consider obtaining them from elsewhere. I may be able to find a post-RT SCFE image if you do not have one at your institutions.

Response: Thank you! An image of post-RT SCFE is now included.

Ed- 4. Minor point: Please change reference numbers in list from superscript to normal font.

Response: Changes have been made in the manuscript.

Reviewer #1:

Major Weaknesses: Imaging examples of some entities like pulmonary and cardiac complications and images for several other entities described in the paper are lacking.
Response: Imaging examples of most entities are now included.

General Comments:

R#1- 1. In figure 7 legend: please put "long TE" next to or in parenthesis after in-phase and "short TE" in parenthesis after out-phase. This is because detection of liver iron on in-phase is function of its longer TE compared to out-phase. This is to avoid any confusion as some of the currently available 3T scanners are not fast enough to give longer TE in-phase, although majority do.
Response: Thank you for pointing out this important concept. Changes have been made in the legend.

R#1- 2. Authors have described many entities representing late complications of cancer therapy, but there are comparatively only few imaging examples. Authors may reduce multiple images of a single particular entity and avoid repetitive examples of same entity, to add images for other entities if available.
Response: Changes have been made in multiple figures with addition of a few.

R#1- 3. Some of the references are duplicated, for example reference 74 and 79 are same; references 45 and 80 are same. Similarly references 86 and 90 are same.
Response: Changes have been made in the manuscript.

Reviewer #2:

R#2- 1. Very well written article.

Response: Thank you.

R#2- 2. At times, the manuscript lacks radiologic detail and reads more like a laundry list of complications. Recommend expanding on description of radiologic findings in some areas particularly less common entities and/or if no accompanying illustrative examples (for example, those associated with cGVHD including findings that mimic primary sclerosing cholangitis, bronchiolitis obliterans as well as in section on pulmonary complications).

Response: Changes have been made in the manuscript. Imaging example of cGVHD with bile duct changes are now included. Bronchiolitis obliterans is already discussed in detail in the first article of this series on acute toxicities.

Specific comments:

R#2- 3. Page 4, line 12: add post treatment to clarify

Response: Changes have been made in the manuscript.

R#2- 4. Page 4, line 22: change women to females

Response: Changes have been made in the manuscript.

R#2- 5. Page 9: bone tumours section: add sentence or 2 about increased risk of malignant bone tumors as well (Roebuck DJ, Radiographics 1999)

Response: Changes have been made in the manuscript.

R#2- 6. Figure 1: recommend eliminating figure 1a

Response: Figure 1a has been removed. Only one figure part (c) has been retained.

R#2- 7. Figure 1: the hypoechoic halo surrounding the solid nodule does suggest a benign lesion in the majority of patients (Hoang, Radiographics). However, it can still be seen in neoplastic lesions (Hoang, Radiographics) and is not included in Bonavita's original description of benign nodules which do not require cytologic evaluation (AJR, 2009)

Response: This discussion is now expanded in the manuscript under thyroid section.

R#2- 8. Figure 2: recommend eliminating as does not add much value

Response: Figure 2 has been removed.

R#2- 9. Figure 3: more figures than necessary, recommend condensing

Response: Figure part (c) is has been removed.

R#2- 10. Figure 4: add details to figure legend regarding time frame between treatment and development of radiation enteropathy

Response: Details have been added in the legend.

R#2- 11. Figure 6: not the best example of hyperintensity on delayed hepatocyte phase MRI as difficult to tell if same lesion as those on T2.

Response: We agree with the reviewer that this is not a great example of hyperintensity of FNH in the hepatobiliary phase. A significant number of FNH show isointensity in the hepatobiliary phase. The larger lesion is subtly seen and marked in this case.

R#2- 12. Figure 8: are there pre therapy images of right kidney – consider adding or mentioning in figure legend that the right kidney was previously normal

Response: Unfortunately, could not find the CT imaging at initial presentation. Changes made in the figure legend.

R#2- 13. Figure 13: unusual osteochondroma, particularly since no attachment to parent bone. Consider using a different example or explain further.

Response: Unfortunately, coronal images are not available in this case. Please guide us on removing this figure.

Reviewer #3:

R#3- 1. Page 2 line 25 …months and onset is usually not seen after 3 years post-transplant…

Response: Changes have been made in the manuscript.

R#3- 2. Page 8 line 24 …to differentiate from residual or metastatic bone disease. As irradiated bone heals…

Response: Changes have been made in the manuscript.

Figures:

R#3- 3. It would be nice to show a breast cancer arising within a radiation field, given this is the most common solid second malignancy.

Response: Unfortunately, we could not find an example.

R#3- 4. It would be nice to show a CT of pulmonary fibrosis within a radiation field pattern for completeness

Response: A figure showing pulmonary fibrosis in the radiation field is now included.

R#3- 5. Figure 1 - delete image 1b – redundant

Response: Figure 1b has been removed.

R#3- 6. Figure 2 - doesn't really add to the presentation – delete

Response: Figure 2 has been removed.

R#3- 7. Figure 13 - do you have a reformatted image showing the osteochondroma in its entirety arising from the adjacent vertebral body/posterior elements. This would better demonstrate your thoughts.

Response: Unfortunately, we do not have coronal CT reformat or coronal MR image available for this case. Please advise us as to whether we can remove this example or not as there is already one example of osteochondroma in the figures.

Tables:

R#3- 8. Table 1 - please standardize format for consistency - list diseases followed by etiology, or etiology followed by possible resultant diseases (both formats are used in current table)
Response: Changes have been made in the table.

Thank you.