Proceedings Article

☐ Tomotherapy: when the patient is a child or an adolescent: hopes, results and issues

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SUMMARY: *We describe our experience in 31 pediatric or adolescent oncological patients (median age 14 years old; range 2-24 years) treated with intensity modulation radiation therapy (IMRT) delivered with linear accelerator (11 patients) or tomotherapy (20 patients). Tomotherapy represents a significant advance in the ability to deliver the high radiation doses that appear to be required to improve the local control of several pediatric tumors. It demonstrated excellent target coverage, homogeneity and organ sparing compared with conventional radiotherapy. Possible disadvantages of tomotherapy in children are also discussed such as increased low dose to non-target tissue, prolonged treatment planning and set-up time, increased anesthesia time and increased overall integral dose.*

KEY WORDS: *Adolescent tumors, Brain tumors, Cranio-spinal irradiation, IMRT, Nasopharynx cancer, Pediatric tumors, Radiotherapy, Sarcoma, Tomotherapy, Whole abdominal irradiation.*

☐ Tomoterapia: quando il paziente è un bambino o un adolescente: speranze, risultati e problematiche

RIASSUNTO: *Riportiamo la nostra esperienza in 31 bambini o adolescenti (età mediana 14 anni; range 2-24) affetti da neoplasie. I pazienti sono tutti stati trattati con radioterapia ad intensità modulata (IMRT) erogata con acceleratore lineare (11 pazienti) o con tomoterapia (20 pazienti). La tomoterapia rappresenta un significativo miglioramento nella capacità di erogare dosi più alte di radioterapia, con l'obiettivo di migliorare il controllo locale di diversi tumori pediatrici. Nella nostra esperienza la tomoterapia, se confrontata con la radioterapia convenzionale, si è dimostrata in grado di comprendere bene ed in modo omogeneo il target. Vengono discussi anche i possibili svantaggi circa l'utilizzo della tomoterapia in età pediatrica: il possibile aumento delle basse dosi a tessuti non-target, i tempi prolungati di trattamento e di set-up, l'aumentato tempo di anestesia ed infine l'aumento della dose integrale all'intero corpo.*

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PAROLE CHIAVE: *Tumori dell'adolescenza, Tumori cerebrali, Irradiazione cranio-spinale, IMRT, Tumori del rinofaringe, Tumori pediatrici, Radioterapia, Tomoterapia, Irradiazione addominale.*

☐ INTRODUCTION

In children, radiation is one of the most effective treatments for solid tumors, yet the threat of its effects on cognition, growth and development has for decades led physicians to seek alternatives to this form of therapy. 3D conformal radiation therapy (3D-CRT) promises high precision in dose delivery and allows approximately 30-40% reduction in the volume of normal tissue included within the high dose volume compared with conventional 2D planning(5). In recent years, the further advancement in conformation has renewed interest in the use of radiation therapy, also in very young children.

Tomotherapy seems one of the most promising methods of treatment. IMRT can achieve an extremely conformal distribution of radiation to the target volume while sparing critical, surrounding normal tissue(6). Because of this ability, the potential for dose escalation exists, which may translate to a better local control without increasing complication rates. Application of these techniques in children is a formidable challenge(7,8,9). Guidelines are developing that ensure appropriate volume for each specific type of tumor, and assessment of outcome is essential to ensure that benefits of the new techniques outweigh the risks. Helical Tomotherapy delivers only IMRT beams with a potential increase in integral dose to normal structures or to the whole body(11). The purpose is to report our preliminary experience with tomotherapy in children with cancer.

☐ MATERIALS AND METHODS

At Centro Riferimento Oncologico (CRO) in Aviano, we implemented in children computerized assisted planning with acquisition of volumetric imaging data in 1995, no-coplanar conformal radiation therapy in 2000, stereotactic irradiation in 2001, IMRT in 2005 and tomotherapy in 2006. A Clinac 2100CD (Varian), equipped with a 120-leaf dynamic multileaf collimator, was used for IMRT planning and 3D conformal radiation therapy. 6 MV X-rays were used for all patients. During every week of treatment, a daily set of isocenter verification portal films were acquired. Helical radiotherapy was delivered with a tomotherapy Hi-Art System, in which a 6 MV linear accelerator and CT technology are integrated. That results in a helical form of radiation delivery, without junctional problems. Through mega voltage CT, images of the patient's anatomy, including tumor characteristics and clinical structures, were acquired daily. This allowed an on-line update of the treatment plan for any change in the patient's anatomy or position.

■ **SIMULATION.** The simulation process was done with helical CT-simulator and took 40-90 min. The upper time limit referred to younger patients that needed sedation or images of the cranio-spinal axis. In order to immobilize the brain we used a thermoplastic mask (sometimes with a dental bite) and for the chest wall and abdomen a combination of a personalized "cradle" bag and extended wing board (Figure 1). After the introduction of tomotherapy the patients were all aligned and immobilized in supine position, also for cranio-spinal irradiation (CSI). The CT images were acquired to a slice thickness and spacing of 5 mm and a pith of 1.5 mm (obtained during quiet respiration).

■ **CONTOURING.** According to ICRU definitions we defined gross tumor volume (GTV), clinical target volume (CTV) referred to the tissue potentially containing a sub-clinical tumor and planning target volume (PTV) to include geometric and set-up uncertainties and the accuracy of the immobilization device used. In some cases we defined the tumor extension determined by CT, NMR and/or PET merged for planning to obtain a metabolic target volume and a dose modulation inside the volume of interest (Figure 2). An extra structure was generated ("tune structure") to obtain a better optimization around the target.

■ **PLANNING.** The IMRT plan was performed on an Eclipse-Varian treatment planning station. The dose was prescribed to a volume (PTV) and not to a single point. The treatment plans consisted preferentially of coplanar fields. The directions of the fields were chosen to avoid normal tissues. For brain tumor we paid special attention to the lenses, cochlea and pituitary area. For other sites we paid special attention to the spine, lungs, heart, bowel, growing bones, glandular and endocrine function. The tomotherapy plan was generated by tomotherapy planning workstation. Prior to optimization, dose volume constraints, precedence, importance and penalty factors were used to

Figure 1. Immobilization devices: thermoplastic mask for brain tumor, thermoplastic mask with a dental bite for nasopharynx cancer and a personalized "cradle" bag for abdominal tumor in a child requiring sedation.

improve target dose homogeneities and reduce doses to normal structure. The dose limits for the critical structure were the standard values used in clinical practice for pediatric tumors. Parameters specified as part of the optimization/dose calculation process were pitch, beam thickness and modulation factor. Film analysis, dose profile comparison and ion chamber measurements were used to verify the intensity maps for each plan and the absolute dose for each patient.

☐ RESULTS

Since the introduction of the intensity modulation program in our Department, we have treated 31 children or adolescent patients with IMRT delivered with linear accelerator (11 patients) or tomotherapy (20 patients) (Table 1).

The median age of patients was 14 years (range 2-24 years). In all cases radiotherapy was part of the multimodality program according to Italian or European pediatric protocol. Young patients affected by tumors that were complex, large, or close to critical areas, were selected for this kind of therapy.

With regard to IMRT and tomotherapy the time required from simulation to the first day of treatment was 1-4 weeks. The time for contouring was 3-10 hours, depending on the necessity to use merged images. From 3 to more than 10 optimization iterations were required. IMRT planning generally required more interactions than tomotherapy. The patients were set-up and treated within a 20-45 minutes period, depending on the volume of the tumor and the need for anesthesia. From the beginning of the tomotherapy program in children we applied a step by step adaptive therapy process including: radiological and metabolic diagnostic imaging, patient position and simulation, target and structure countering, treatment planning optimization, radiotherapy imaging "on board", planning and treatment images co-registration, modified patients position, treatment delivery and a modified treatment plan, if necessary.

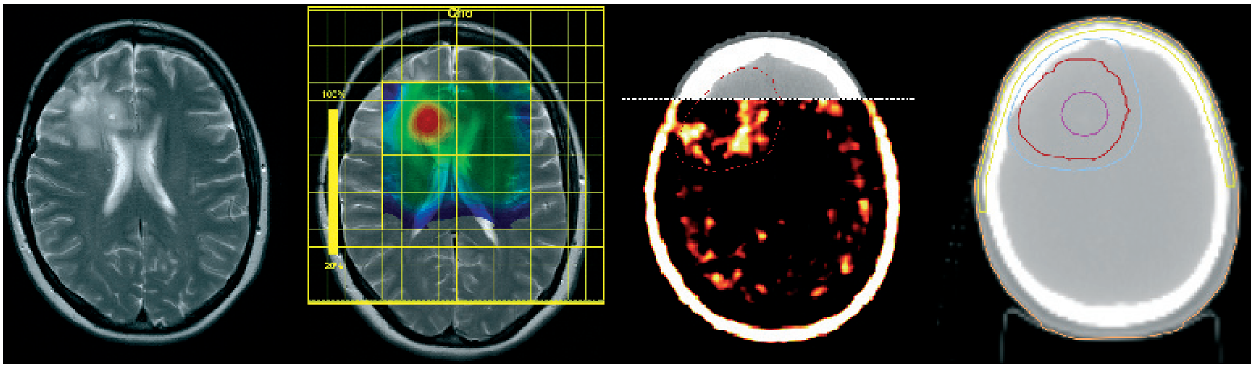

Figure 2. Tumor extension in a frontal malignant gliomas determined by CT, NMR (*blue line*), spectroscopic NMR (*fuchsia line*) and PET-CT (*red line*) merged for planning.

	IMRT	Tomotherapy
• CNS tumors	3	8
• Sarcoma	5	5
• Nasopharynx	1	1
• Whole abdominal	1	1
• Lymphoma		2
• Others cancers	1	3
Total	***11***	***20***

Table 1. Number of pediatric or adolescent patients treated, since May 2005 until May 2007, with IMRT delivered with Linear Accelerator or Tomotherapy.

❒ ADVANTAGES

■ ***INCREASED CONFORMALITY.*** Therapeutic doses of radiation delivered to a child may have devastating side-effects, especially in view that there may be long-term survivors. Certain normal organs in children are significantly more sensitive to radiation than in adults, e.g. brain, bone growth, endocrine functions(14). From our experiences, tomotherapy has enabled to deliver more precise high dose radiation to the tumor and spare normal tissue.

In *brain tumors* tomotherapy, with computer assisted optimization of treatment planning, is able to maximize delivery of radiation dose to the tumor while minimizing the dose to the normal tissue (e.g. shielding optic chiasm, lens and pituitary gland) and to the rest of the brain (Figure 3). This is particularly important in very young children. Neural tissue is characterized by a rapid postnatal growth that slows in late infancy and ceases in adolescence. The skeletal pattern has its peak growth rate in early postnatal period and during puberty. Recognition of the mechanism of organ growth allows better identification of relative radiosensitivity.

In 3 *cranio-spinal irradiation* patients the inspection of dose-volume histograms reveals excellent conformality for the CTV brain, CTV cord, and dose to the organs at risk is uniformly low (Figure 4). The helical nature of the beam delivery eliminates the need for junction lines between cranial and spine fields. The fall-off dose in the vertebral body is uniform in all directions in comparison with the conventional treatment in which there is a non-symmetric dose gradient and a higher chance of asymmetric bone development (Figure 5).

Tomotherapy has also been applied in our experience on a small recurrence ependymoma, that could also have been eligible for stereotactic radiotherapy. In this case *stereotactic tomotherapy* was a good alternative to the traditional system that provides the use of relocatable and sometimes uncomfortable, stereotactic frame.

In a young patient with *nasopharyngeal cancer* tomotherapy enabled to decrease the dose to the parotid glands and to the auditory apparatus with the aim of reducing the incidence of xerostomia and hearing loss, which will certainly improve the quality of life(6,14). At the same time, it has permitted to deliver simultaneous modulated radiation therapy boost to the metabolically active areas (Figure 6).

In *soft and bone tissue sarcoma* the opportunities offered by tomotherapy are very encouraging to limit the dose to organs at risk such as eyes, spinal cord, rectum wall, bladder, bowel and bone. Tomotherapy planning was performed on 4 children with soft tissue

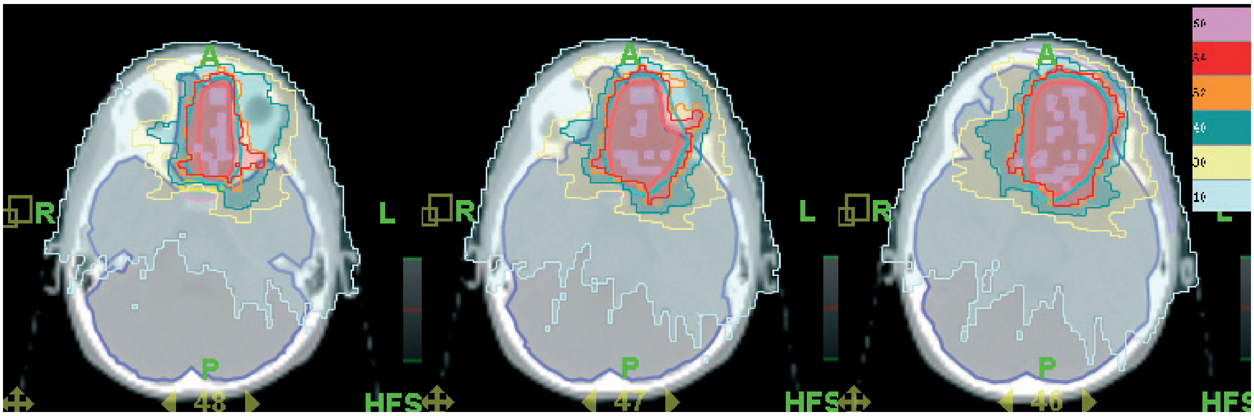

Figure 3. Tomotherapy plan in a frontal malignant rhabdoid tumor, close to chiasmatic area and to cribriform plate.

sarcoma (2 bladder-prostate, 1 leg, 1 paraspinal tumor) and 1adolescent with a bone tumor close to the hip. The bladder-prostate patients were respectively 2 and 4 years old. For both acute toxicity was negligible.

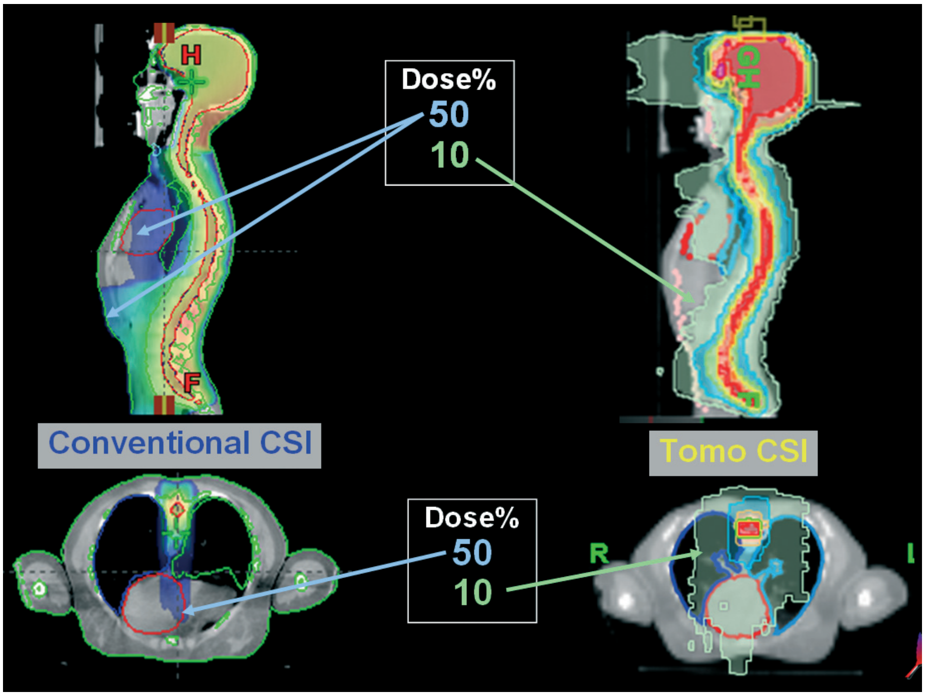

Figure 4. Differences in dose distribution to organ at risk between conventional CSI and tomotherapy CSI. Tomotherapy gives lower doses to larger volumes and higher doses to smaller volumes.

Treatment of the whole abdomen in *Wilms' tumor* represents a new application of tomotherapy. Here, the goal in advanced abdominal disease is to treat the retroperitoneal lymph nodes and the peritoneal surface while reducing the dose to kidney and bone marrow. Typically, 15 Gy in 10 daily fractions are given to the whole abdomen, for patients with post surgical abdominal residual disease or tumor rupture. An anterior-posterior beam is used, arranged with posterior shielding of the residual kidney at 12 Gy. Tomotherapy provided adequate coverage of the peritoneal cavity while limiting the dose to the residual kidney, spinal cord and bone marrow.

Comparing IMRT and tomotherapy plan, the dose to the PTV was less homogenous for IMRT (mean dose to PTV 108%: range 60-120%) compared with tomotherapy (mean dose to the PTV 98%: range 73-115%). For a prescription dose of 15 Gy the kidney received lower than 25% and 50% of total dose with tomotherapy and IMRT respectively. The mean dose to all bones was reduced in favour of tomotherapy (Figure 7).

■ ***DOSE ESCALATION.*** Another advantage of tomotherapy is the potentiality for dose escalation. A 13-year-old female, with a recurrence paraspinal cordoma (C7-D3) was treated with tomotherapy in 33 daily fractions. The dose was modulated in the spinal cord (45 Gy), in the paraspinal area close to the spinal canal (54 Gy) and finally in the area containing macroscopic disease (66 Gy).

■ ***MEGAVOLTAGE CT.*** Using tomotherapy set-up is indexed to fixed internal landmarks rather than external skin marks for daily patient positioning(10). Megavoltage CT permitted discovering a mistake in contouring the spinal canal due to the presence of metallic spinal stabilization bars, on the first day of treatment.

Through adaptive therapy process the different position of the organ at risk was evaluated and treatment promptly modified (Figure 8). Any tumor shrinkage during a course of radiotherapy can also be detected and lead to a change in anatomy and finally to the target volume.

❐ POTENTIAL PROBLEMS

There are several potential roles for tomotherapy in the management of pediatric tumors. However, the precise impact of tomotherapy on long term therapeutic ratio for children is not clear.

■ ***INCREASED LOW DOSE TO WIDE AREA.*** The high grade of conformity of the target volume to the tumor shape involves multiple, nearly unlimited fields. So the potential increase in integral dose to structures or to the whole body is an issue of concern(1,4,10,11,12). It has

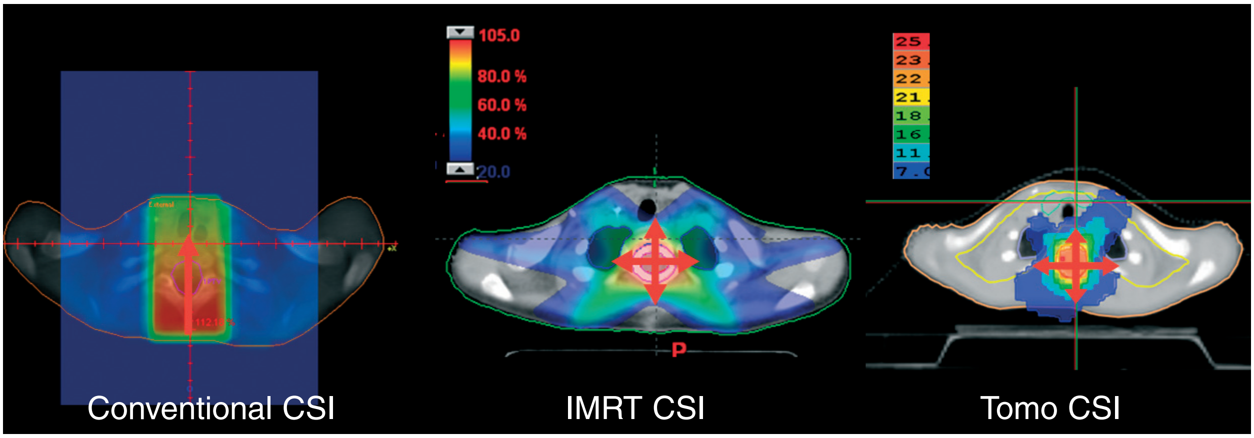

Figure 5. The fall-off dose in the vertebral body comparing conventional CSI (*non symmetric*) and, IMRT and tomotherapy CSI (*symmetric*).

been estimated that the integral dose of tomotherapy CSI is 6.5% higher than conventional CSI. Comparing DVH analysis of conventional CSI with tomotherapy plan, the latter gives lower doses to larger volumes and higher doses to smaller volumes. This is true not only for tomotherapy but for other IMRT techniques (Figure 4, 5).

Such increase may result in an increase in the rate of secondary malignancies(2). Also the number of monitor units was higher for tomotherapy respect to conventional radiation therapy or IMRT delivered with linear accelerator.

Some Authors concluded that IMRT increased the risk of secondary malignancies as compared to conventional radiotherapy from approximately 1 to 1.75% for patients surviving 10 years(3,10).

■ ***PROLONGED TREATMENT TIME, SET-UP AND PLANNING.***

IMRT and tomotherapy are "multi-step" processes. Careful consideration throughout the entire process is necessary to ensure that an optimal treatment plan is delivered. We usually reserve 7 working days for treatment planning because of this high level of complexity. In this time generally most physicists and oncologists review multiple plans.

The use of a narrower fan beam and pitch as well as an increased modulation factor would facilitate better conformality. But the clinical use of these parameters would result in nearly doubled treatment times (20 minutes using a 25 mm fan beam vs 32 minutes using a 10 mm fan beam for tomotherapy CSI in a 3-year-old child).

The time necessary for setup with megavoltage CT is about 5-7 minutes. For children requiring sedation,

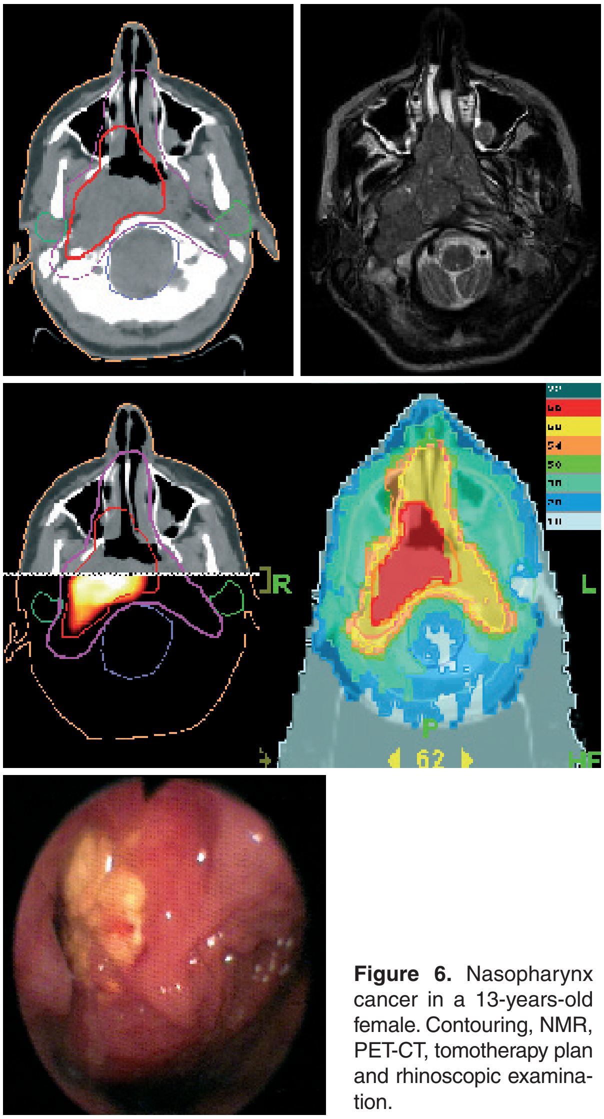

Figure 6. Nasopharynx cancer in a 13-years-old female. Contouring, NMR, PET-CT, tomotherapy plan and rhinoscopic examination.

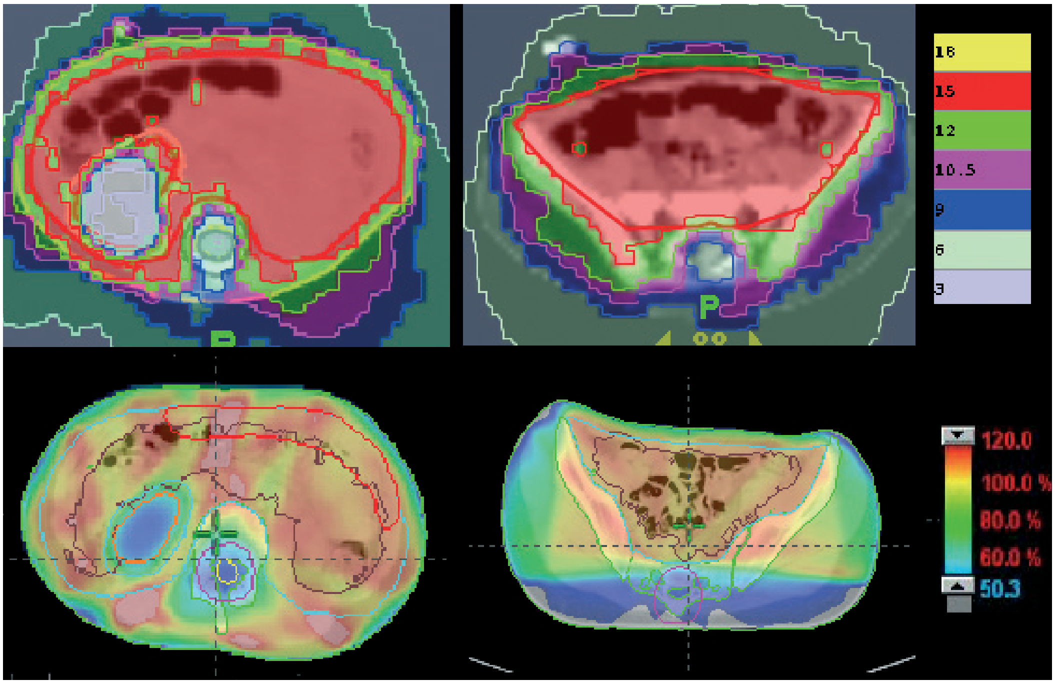

Figure 7. Whole abdomen irradiation. The upper images refer to a patient treated with tomotherapy. The lower images refer to a patient treated with IMRT delivered with linear accelerator. Note the different homogeneity in the target volume between two kinds of plan.

remote monitoring without access to the patient for this length of time may be of concern. Moreover auxiliary support including anesthesia also require time and, in combination with tomotherapy treatment delivery, occupies al least 1 hour of tomotherapy room time.

☐ CONCLUSIONS

Combined modality approach in pediatric oncology has served as a model for much of the cancer treatment today. Successful implementation of this new radiotherapy technology will depend on the results of prospective assessment of functional outcomes and local control of diseases. Our aim will be to continue to develop IMRT with linear accelerator or tomotherapy for children with solid tumors that yields similar or slightly better target coverage than 3D-CRT and significant improvements in normal tissue doses. Our preliminary experience suggests a greater sparing of critical normal structure and a better PTV homogeneity using IMRT in comparison with 3D-CRT, especially in children with large and complex target volu-

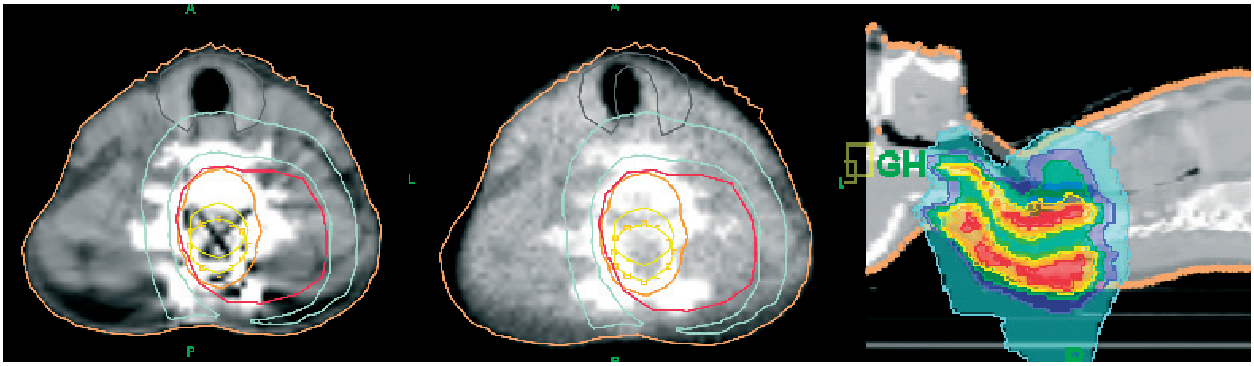

Figure 8. Megavoltage CT used for “adaptive therapy process” in a young girl with metallic spinal stabilization bars. Note the difference in spinal cord contouring between diagnostic CT (*yellow line*) and megavoltage CT (*yellow line with shapes*). On the right tomotherapy plan.

me. Concerns regarding the risk of radiation induced cancer, as a consequence of an increase in low dose radiation exposure, needs to be carefully addressed.

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