Clinical experience in pediatric neuroblastoma intensity modulated radiotherapy

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Abstract

Background: In spite of the numerous publications of dosimetric comparison of intensity modulated radiotherapy (IMRT) versus conventional radiotherapy in pediatrics, few data exist regarding clinical use of IMRT and its potential late effects.

Procedure: Pediatric neuroblastoma patients treated between November 2008 and October 2010 with IMRT were reviewed. Treatment plans, clinical, laboratory and radiological data at the last follow up date were evaluated.

Results: Thirteen patients received IMRT. The mean age was 4.9 ± 2 years. The radiation dose ranged from 21 to 25.5 Gy with a mean dose of 24.06 Gy. The mean liver dose was 9.81 Gy. The V8 of the liver was 51 ± 20%, and the V15 of the liver was 21 ± 12%. V18 of the right and left kidneys were 32 ± 27% and 23 ± 18% respectively. The minimum and maximum vertebral point doses were 12.82 and 24.87 Gy respectively. The IMRT treatment was well tolerated in terms of acute toxicity. At 26 months follow up, second malignancy and skeletal asymmetry were not noted, and the liver and kidney functions showed no significant abnormalities.

Conclusions: The use of IMRT in pediatric neuroblastoma confers higher target conformity with better sparing of the kidneys and it did not show any considerable short term side effects.

Introduction

The use of radiation therapy (RT) either preceding or following bone marrow transplantation in high risk neuroblastoma (NB) has been shown to decrease local recurrence rates [1,2]. Studies that incorporated local RT with autologous stem cell transplant have shown excellent local control rates above 80% [3]. A study from the Children’s Cancer Group showed a dose–response relationship with respect to local control, with 20 Gy to the primary site having a better locoregional control rate compared to 10 Gy [4].
Most of the current pediatric NB protocols recommend RT doses in the range of 21–36 Gy. These are doses that usually approach, sometimes exceed, the kidney tolerance dose [5]. NB tumors are often located in the midline and paraspinal regions, thus encroaching on one or both kidneys. The problem is compounded by the use of cisplatin chemotherapy, a known nephrotoxic agent, and RT dose to the kidneys must be kept to the minimum to avoid renal injury.

IMRT has been recently used in the treatment of pediatric cancer and has the potential to reduce the RT dose to the organs at risk (OAR) adjacent to the tumor, at the expense of an increase in the normal tissues volume exposed to low RT doses [6]. Despite IMRT has been widely used in many tumor sites in adults like head and neck cancer [7] and prostate cancer [8], its use in the pediatric field remains unclear, as there is substantial lack of knowledge of the potential late side effects and toxicity, particularly the risk for second malignant tumors (SMT) in this young age group.

At King Faisal Specialist Hospital and Research Center (KFSH&RC), we have started to use IMRT in the treatment of abdominal NB since 2008, in order to reduce the RT dose to the kidneys. We identified 13 NB patients treated with IMRT. To the best of our knowledge, this is the largest published series of IMRT treated NB patients from a single institution. Most of other published series included IMRT-dosimetric comparisons on virtual planning rather than actually IMRT-treated patients.

The aim of this work is to review and evaluate the IMRT plan, assess the dose to the critical structures, and report treatment toxicities in this young group of patients.

Materials and methods

Throughout the period from November 2008 to October 2010, patients treated at our center for abdominal NB were reviewed to select patients treated by IMRT. For each patient the plan was evaluated regarding the total dose, the target coverage, the dose to the kidneys, liver, vertebral body and the low dose to normal tissues.

The patients were treated according to a modified COG protocol 3891 for high risk NB with 6 cycles of induction chemotherapy followed by surgical resection. This was followed by consolidation myelo-ablative chemotherapy, autologous stem cell transplant (ASCT), and localized abdominal RT. In the early years, total body irradiation (TBI) was used as a part of the pre-conditioning regimen, which was later changed to chemotherapy only-based conditioning regimen. Because of the young age, most of the children received radiation treatment under general anesthesia (GA).

The selection of the optimal RT technique was based on the decision of the treating physician. The IMRT plan was compared with the 3D-CRT-plan, and IMRT treatment was implemented when the 3D-plan could not achieve the required RT dose constraints, namely in terms of renal dose. The target dose ranged from 21 to 24 Gy for completely resected tumors, while higher doses were prescribed for gross residual disease.

The gross tumor volume (GTV) was contoured on the axial slices based on the preoperative post-chemotherapy CT scan, and the planning CT. An additional 1.5 cm margin was added to generate the clinical target volume (CTV). This margin was then edited to include only 2 mm of the kidneys and the liver. Finally, the CTV was expanded by 10 mm margin cranio-caudally, and by 3 mm in the lateral and antero–posterior directions to generate the planning target volume (PTV). A plan was accepted if at least 99% of the PTV was covered by the 95% isodose volume, and maximum hot spots were <110%. For the OAR, the primary objective criteria entailed more than 80% of at least one kidney received less than 18 Gy, and less than 50% of the liver volume received more than 8 Gy [V8 Gy], and the volume of the liver receiving more than 15 Gy [V15 Gy] was less than 25%.

The vertebral body was marked as a secondary target volume aiming at delivering as much homogeneous dose as possible within the bony tissue of the adjacent vertebrae with a minimum dose of 15 Gy and a maximum dose as low as possible so as to avoid potential asymmetric skeletal growth in the future.

Treatment was delivered using Linac 6–10 Mv. Cone beam CT (CBCT) was regularly done in the first 3 treatments then once weekly.

The patients underwent regular follow up and were assessed for the local control, liver functions, renal functions, and other events [skeletal growth asymmetry, veno-occlusive disease (VOD), and second malignancy].

Results

Out of 17 patients treated with postoperative RT for abdominal NB, 13 patients received IMRT. At the time of starting radiotherapy the mean age was 4.9 ± 2 years. There were 7 males and 6 females. All patients were treated for high risk disease. The radiation dose ranged from 21 to 25.5 Gy with a mean dose of 24.06 ± 1.16, using a daily fraction 1.5–1.8 Gy. One patient received initial 12 Gy TBI, followed by 12 Gy local abdominal RT [24 Gy total tumor dose], and the reported RT doses were relevant to the plan sum. All other patients received no TBI. Two patients were treated with rapid arc (RA) and 11 patients were treated with IMRT using 5–7 fields.

The PTV volume ranged from 63 to 905 cc with a median volume of 402 cc. Table 1 summarize the volume, median of the means dose, range of the means dose and D-max for the PTV, liver, right and left kidneys. The median PTV for central midline tumors was 402 [range 85–905] cc as compared to 241 [range 63–581] cc for lateralized tumors.

The irradiated fractional volumes of the liver and kidneys were compared at different dose levels, 18 Gy for the kidneys and 15 Gy for the liver. We also looked at the V8 liver, as a threshold dose for occurrence of VOD in transplanted patients. The mean liver volume was 529 cc, and the mean dose was 9.81 Gy. Higher mean liver doses [up to 17.10 Gy] were accepted in individual cases, when the tumors were in close proximity to the liver. The V8 of the liver was 51 ± 20% and the V15 of the liver was 21 ± 12%.

We looked at both kidneys as bilateral structures and as one total volume; the mean kidneys volume was 105 cc, with a D-max of 27.06 Gy and a mean dose of 14.40 ± 2.65 Gy. The V18 of both kidneys was 31 ± 13%, V18 of the right kidney was 32 ± 27% and V18 of the left kidney was 23 ± 18%.

The maximum dose to the spinal cord was 23.16 Gy and the maximum dose to the vertebral body was 24.87 Gy. The minimum dose of 15 Gy [V15 Gy] was less than 25%.

Finally, the CTV was expanded by 10 mm margin cranio-caudally, and by 3 mm in the lateral and antero–posterior directions to generate the planning target volume (PTV). A plan was accepted if at least 99% of the PTV was covered by the 95% isodose volume, and maximum hot spots were <110%. For the OAR, the primary objective criteria entailed more than 80% of at least one kidney received less than 18 Gy, and less than 50% of the liver volume received more than 8 Gy [V8 Gy], and the volume of the liver receiving more than 15 Gy [V15 Gy] was less than 25%.

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respectively. Fig. 1 shows DVH of one patient, illustrating the dose to the PTV and the adjacent vertebral body.

The follow up duration ranged from 1.2 to 26 months with a median follow up of 19 months. One patient was lost to follow-up shortly after radiotherapy. Three patients had documented death at the time of analysis, one died 7 days post-transplant with septic shock, and another patient died 6 months post radiotherapy from progression of distant metastasis. The third patient died 3 months post radiotherapy from both local and systemic disease progression. Eight of the remaining 9 patients [89%] have their local disease well controlled at the time of the last FU.

**IMRT compared to 3D-conformal RT**

We evaluated the normal tissue (NT) volumes receiving 2, 5 and 10 Gy-isodose level [V2, V5, V10] for IMRT and 3-DCRT in three patients. Table 2 shows the dosimetric comparison of IMRT versus 3 fields CRT [patient #1&3], and IMRT versus conventional AP/PA fields [patient #2]. The patient #3 re-

### Table 1

Summary of the dosimetric parameters for PTV, kidneys and liver in IMRT treated patients.

<table>
<thead>
<tr>
<th>Volume (cc)</th>
<th>Mean dose</th>
<th>D-max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>Range</td>
<td>Median</td>
</tr>
<tr>
<td>PTV</td>
<td>402</td>
<td>63–905</td>
</tr>
<tr>
<td>Liver</td>
<td>541</td>
<td>280–767</td>
</tr>
<tr>
<td>Rt kidney</td>
<td>52</td>
<td>26–85</td>
</tr>
<tr>
<td>Lt kidney</td>
<td>60</td>
<td>25–84</td>
</tr>
<tr>
<td>Both Kidneys</td>
<td>102</td>
<td>61–156</td>
</tr>
</tbody>
</table>

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**Figure 1** DVH showing a homogenous vertebral body [VB] dose lower than the PTV dose.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Dosimetric evaluation of 3D versus IMRT for normal tissues, the kidneys and the liver (N = 3 patients).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient #1 CRT-3 Fields</td>
<td>Patient# 1 IMRT</td>
</tr>
<tr>
<td>V2 Gy</td>
<td>2461 cc</td>
</tr>
<tr>
<td>V5 Gy</td>
<td>2216 cc</td>
</tr>
<tr>
<td>V10 Gy</td>
<td>1847 cc</td>
</tr>
<tr>
<td>Kidney V18 Gy</td>
<td>80%</td>
</tr>
<tr>
<td>Kidney Mean</td>
<td>21.14 Gy</td>
</tr>
<tr>
<td>Liver Mean</td>
<td>12.43 Gy</td>
</tr>
<tr>
<td>Liver V8 Gy</td>
<td>58%</td>
</tr>
<tr>
<td>Liver V15 Gy</td>
<td>45%</td>
</tr>
</tbody>
</table>

*Patient 3 received 12 Gy TBI + 12 Gy local XRT, the figures represent sum plan.*
ceived 12 Gy TBI as part of preconditioning regime in addition to post-transplant 12 Gy to the primary site for local control, and the figures displayed are pertinent to the plan sum [TBI + primary tumor bed]. Whereas the dose to the liver was higher with IMRT as compared to 3D-conformal RT, a clear dosimetric advantage could be seen for IMRT in terms of the kidneys. Using IMRT, the kidney volume receiving 18 Gy was reduced by 20–50%, and the mean dose was marginally reduced.

RA was slightly better than IMRT in terms of PTV coverage and dose to the kidneys. The main advantage of RA was reduced treatment time and faster treatment delivery, which shortened the GA duration, since most of the patients were treated under GA. The volume of normal tissues receiving low dose radiation [NT = body minus PTV] was much less with 3-DCRT as compared to IMRT, for the dose range of 2–5 Gy. This pattern was maintained until the DVHs intersected at doses above 8–10 Gy (Fig. 2).

Acute toxicity

All patients received daily oral or IV Ondansetron 1 hour prior to radiotherapy. One to two episodes of vomiting were reported by five patients on the first day of treatment as they did not receive Ondansetron before treatment, while none of the patients complained of vomiting with adequate medications. Skin grade I erythema was noticed in most of the patients, only two patients have developed grade II dry desquamation after the second week of treatment. Grade 3 toxicity was not reported. None of the patients complained of diarrhea. Grade III hematological toxicities were not seen.

Late toxicity

The follow-up period is too short for late toxicity evaluation. At a 26 months [median 19 months] follow up period, no second malignancy has been noted. Evaluation of the patients did not show so far any skeletal abnormality on the FU X-rays and CT scan. The liver functions were normal in all except 2 patients who died from post transplant septic shock [first] and visceral metastasis [second]. The remaining 11 patients had normal liver enzymes and bilirubin level, with mean ALT 31 ± 26 U/L of and mean bilirubin of 7+/3 umol/L. One patient who died from post transplant septic shock had elevated creatinine. All of the remaining patients had normal renal functions [mean creatinine level of 31+/15 umol/L], and normal contrast enhancement evaluation of the kidneys on FU CT scan.

Discussion

The radiotherapy dose for NB local control varies according to the treatment protocol: the CCG A3973 protocol prescribes 2160 cGy, while the German NB 2004 trial advises 36–40 Gy plus MIBG therapy. At our institution, patients with completely resected tumor received a dose of 21–24 Gy, with a boost dose up to 36 Gy in patients with gross residual tumor, if this could be achieved without exceeding the kidneys tolerance.

The mean PTV for central midline tumors was 417 [range 85–905] cc as compared to 262 [range 63–581] cc for lateralized tumors. The patients with centrally located tumors were more prone to have larger residual disease. Because the fact that centrally located tumors were often attached to or wrapping around the major vessels and nerves, achieving a total or subtotal resection was not possible. The large PTV added to the complexity of RT planning and the difficulty of reducing the RT dose to the kidneys in this group of patients.

Whether the PTV should include the vertebral body or not and rather be limited to the target is one of the controversial areas in IMRT planning for NB. To the best of our knowledge, there exists no outcome data on late effects in the literature to support the use of IMRT in NB. Paulino et al. compared conventional to IMRT plans, with and without the vertebral body being included in the PTV. The plan that excluded the vertebra from PTV showed heterogeneous dose distribution over the vertebral body with consequential unidentified long term skeletal side effects [9]. In this young age group of patients, doses
as low as 18 Gy have been associated with an increased risk of scoliosis. On the other hand, including the vertebral body in the primary PTV to doses above 20 Gy makes it very difficult to reduce the dose to the kidney. Hence, we elected to contour the vertebral body as a secondary PTV, in order to avoid significant heterogeneous dose gradient across the vertebra that could result in skeletal deformities in the future while reducing the dose to the kidneys.

The evaluation of liver and kidney toxicities as a function of time is a complex endpoint, since these organs may sustain subclinical damage that may be only expressed later on. This is particularly true for this group of transplanted children, where the potential toxicity of high-dose chemotherapy could be an additional contributing factor. Due to the retrospective nature of this study we could only evaluate the toxicity based on the kidney and liver functions, as well as the routine post-treatment follow-up CT scan with contrast.

The potential of developing SMN is a major concern in this young patient population. Hall and Wuu have hypothesized that the use of IMRT will likely result in an increase in secondary malignancies from 1% using conventional RT to 1.75% using IMRT for patients surviving 10 years from irradiation. This is because more normal tissue is receiving low dose RT with IMRT compared to conventional RT, and more monitor units are used to deliver the same dose with IMRT which translates to more radiation leakage to the entire body [10]. Hall also suggested that children are more sensitive than adults for developing SMN by a factor of 10. It is not possible to make conclusions from our data on the effect of IMRT on second malignancy due to the short duration of the follow up period. In the current study, a dosimetric comparison of IMRT to conventional RT for 3 NB patients is displayed in Table 2. For volumes exposed to low-dose RT, IMRT significantly increased the normal tissue volume receiving 50% or less of the prescribed dose. This must be cautiously considered when implementing IMRT in pediatrics, particularly with extended RT fields such as craniospinal or mantle fields, where a significant volume of normal tissues would be encompassed.

Conclusions

The use of IMRT in pediatric NB confers higher conformality to the target volume with better sparing of the kidneys, particularly in patients with centrally located tumors. This is achieved at the expense of a larger volume of normal tissues receiving low RT dose. In this study as in others using IMRT in pediatric and young patients, there is a need for a longer follow-up for more reliable estimation of potential hazards of IMRT with respect to late skeletal toxicity and secondary malignancies.

References