Intensity Modulated Radiation Therapy in Pediatric Cancer; Clinical Outcome and Risk of Radiation-induced Malignancies

Nan Suntornpong, M.D.
Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Intensity modulated radiation therapy (IMRT) allows modulation of beam intensity within treatment fields for conformal RT providing superiority in terms of target coverage, conformity and minimizing dose to organs at risk. Although the risk of secondary malignancies may be increased by IMRT, the outcome in pediatric cancers such as neuroblastoma, rhabdomyosarcoma and medulloblastoma have been reported with acceptable local control and toxicities.

Keywords: Intensity modulated radiation therapy, pediatric cancer

Siriraj Med J 2015;67:41-45
E-journal: http://www.sirirajmedj.com

INTRODUCTION

Intensity modulated radiation therapy (IMRT) is one of the advanced radiation therapy (RT) techniques that allows modulation of beam intensity within treatment fields for highly conformal RT delivery. The steep dose gradient in IMRT provide superiority in terms of target coverage, conformity and minimizing dose to organs at risk. However, there are concerns that risk of secondary malignancies may be increased by IMRT. This article provides an overview of radiation- induced secondary malignancies and IMRT outcomes in some pediatric cancers to encourage the use of advanced RT technique in children with awareness of its risk.

Correspondence to: Nan Suntornpong
E-mail: sirdoffice@gmail.com
Received 8 September 2014
Revised 14 November 2014
Accepted 1 December 2014

In general, secondary malignancies can be induced by RT in long-term survivors from cancer. Brenner et al reported data from National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program. The absolute risk of secondary malignancies caused by RT is 1.4% for patients surviving more than 10 years.[1]

Radiation-induced carcinomas are observed in the lining cells of the body and in tissues remote from the radiation field that received lower doses. Carcinogenic risk seems to be highest for dose less than 6 Gy. However, radiation-induced sarcoma developed in tissues receiving higher doses in or close to the radiation fields. Therefore, sarcoma has not been found in atomic bomb survivors who receive less radiation dose.[2,3]

For children, several reasons should be aware in radiation-induced secondary malignancies which includes:

1. Variation in lifetime risk of radiation-induced cancer is a function of age. The average

risk is 4% per Sv of radiation-induced cancer which is found for all ages with almost 15% per Sv for a young female and 1% per Sv for age 60 age years and older.

2. Radiation scattered from treatment volume of RT in adults and children is the same, but is more significant in children due to smaller size of body.

3. Several pediatric cancers involve germline mutation which may increase sensitivity for radiation –induced cancer.

IMRT may increase incidence of second malignancies in the patients who received this advanced technique because of 2 reasons.

1. IMRT spreads out a lower radiation dose to a larger volume of normal tissues which is a carcinogenic radiation dose.

2. IMRT requires more monitor units for modulated field. The increase in monitor units results in greater head scatter in a linear accelerator leading to greater entire body dose.

Kry et al reported 3.5-4.9 times of monitor units to deliver by IMRT compared to conventional RT in prostate cancer. The maximum risk of fatal second malignancy was 1.7, 2.2 and 5.1% for conventional RT, IMRT using 10 Megavoltage and IMRT using 18 Megavoltage respectively.[4]

Currently IMRT for pediatric cancers have been used in many diseases. The outcomes in neuroblastoma, rhabdomyosarcoma and medulloblastoma have been shown due to ability to spare critical organs to reduce late treatment effects.

Neuroblastoma

Neuroblastoma (NB) comprises of 8-10% of all pediatric neoplasms. Standard treatment includes intensive chemotherapy and aggressive surgery. RT to primary site has been used for consolidation therapy in high risk patients. Local failure is still significant with 16-33% rate for this group of NB.

The kidney and spine are important dose-limiting organs for abdominal RT in NB. IMRT is used to increase dose gradient between these structures and target tissue. Currently, dose 21-24 Gray (Gy) is required to treat microscopic disease while maximum 14.4 Gy is limited to ipsilateral kidney in high risk NB. Additionally, cisplatin which is used in NB also is a nephrotoxic agent. A study by Pai Panandiker et al showed no locoregional failure in high risk NB patients treated by IMRT 23.4-36 Gy. The 2- year event-free survival was 58.5%. The mean follow up time of 2.2 years was not sufficient for late effects.[5]

Paulino et al compared 3 RT techniques for high risk abdominal NB between parallelopposed anteroposterior fields and 2 different IMRT. The result showed that IMRT lowered mean dose 10-15% to bilateral kidneys in the patients with midline tumors, but increased mean dose to contralateral kidney in the patients with lateralized tumor. Additionally, IMRT delivered higher mean dose to spleen, liver and stomach over conventional RT.[6] For spine, IMRT with inclusion of adjacent spines in CTV showed more dose homogeneity to vertebral bodies compared to without inclusion of spine in CTV. No long term skeletal side effects or secondary malignancies were observed in this report.

Rhabdomyosarcoma

Rhabdomyosarcoma (RB) arises from skeletal muscle which is found in several sites such as head and neck region, genitourinaty tract, trunk and extremities. Important prognostic factors include histologic subtype and primary tumor sites. Standard treatment is chemotherapy with RT and/or surgery. The recommended RT dose is in the range of 36-50.4 Gy with 80-95% 5-year

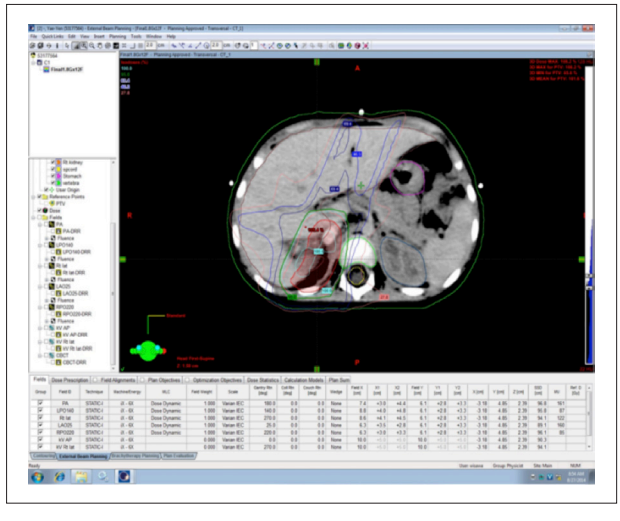

Fig 1. Shows an example of IMRT plan for isodose distribution in a patient with neuroblastoma following chemotherapy and surgery

locoregional control in the International Rhabdomyosarcoma Study (IRS) IV which depends on sites. Parameningeal head and neck region, including nasopharynx, nasal cavity, paranasal-sinuses, middle ear or mastoid, pterygopalatine or infratemporal fossa and parapharyngeal space are subsites with poor prognosis. This is due to risk of intracranial extension and cranial nerve involvement.

Lin et al reported result of Children Oncology Group (COG) D9803, the first comparative study between IMRT and 3DCRT in intermediate risk rhabdomyosarcoma. There were no differences in 5-year locoregional control and failure – free survival between the 2 RT techniques. The coverage of IMRT planning treatment volume was significantly greater for IMRT than 3DCRT patients. There was no significant difference in volumetric data receiving 5, 10 and 20 Gy (V5,V10 and V20 respectively) for brain, optic chiasm and pituitary gland in all head and neck sites between the 2 techniques. For median follow-up time 5.7 and 4.2 years for 3DCRT and IMRT respectively, no significant difference in secondary malignancies developed.[7]

Yang et al reported result of IMRT and chemotherapy in parameningeal RB which is subsites with early recurrence and poor prognosis. IMRT using a dose-painting technique has been shown to produce superior sparing of critical organs compared with sequential IMRT with more conformal dose distributions. The 5-year local failure-free survival in 47 patients was 86%. Age, histology and time to RT did not affect local failure risk. The 5- year central nervous system failure –free survival was 85%.[8,9]

Medulloblastoma

Medulloblastoma is the most common malignant tumor of central nervous system in children. Standard treatment consists of surgical resection followed by RT and chemotherapy. RT to entire neuraxis is indicated in medulloblastoma with several long-term effects such as neurocognitive deficit, hearing impairment and endocrine dysfunction. Craniospinal irradiation (CSI) has evolved to improve outcome and decrease these toxicities in this challenging RT technique.

Parker et al reported the superiority of PTV coverage, dose homogeneity and organ risk sparing by IMRT in medulloblastoma compared to standard 2DCRT and 3DCRT techniques. The integral dose for IMRT and 3DCRT techniques were quite similar.[10]

Kusters et al also reported better target coverage, homogenous dose distribution in junction and better normal tissue sparing in CSI by daily intrafractionally modulated junction IMRT compared with 3DCRT in 5 medulloblastoma patients.[11]

Ototoxicity in medulloblastoma is a significant complication caused by combination of cisplatin and RT. RT technique to limit cochlea dose has been developed. Although the exact mechanism of synergistic effect remain speculative, posterior fossa boost by IMRT showed lower incidence of grade 3 or 4 hearing loss compared to that of conventional RT (13% and 64% respectively) in a study by Huang et al. IMRT delivered 68% of radiation dose to auditory apparatus compared to conventional RT without disturbance to target volume dose. Although threshold of cochlea tolerance has not been established in combined treatment in medulloblastoma, younger age may be more sensitive to ototoxicity than adults.[12] Paulino et al found statistically significant difference in mean radiation dose to cochlea according to degree of ototoxicity in patients treated by IMRT and cisplatin-based chemotherapy with dose to cochlea increasing severity of this complication.[13] IMRT boost to tumor bed has been developed in medulloblastoma to limit ototoxicity from posterior fossa boost. In terms of local control, concern for marginal failure is more important in IMRT than in conventional RT and 3DCRT. Paulino et al also reported no excess failure in non-tumor bed posterior fossa from tumor bed boost by IMRT in standard risk patients.[14]

Polkinghorn et al reported excellent local control in both standard and high risk patients with limited boost to tumor bed with no isolated posterior fossa relapse out of boost volume. Low mean dose to cochlea resulted in only 6% of grade 3 hearing loss without any grade 4 at median follow up 19 months.[15]

Neurocognitive impairment is one of the

late effects in MB patients especially those of younger age. RT to temporal lobe can affect the main critical structure for cognitive risk, the hippocampus. The correlation between dose to temporal lobe and hippocampus and neurocognitive outcome have been shown.[16,17] The effect of RT to subventricular zone of lateral ventricles for neurocognitive junction is less clear. Blomstr et al showed outcome of protecting neurogenesis in developing brain from 4 RT techniques in MB. These included standard opposing fields, IMRT, intensity modulated arc therapy (IMAT) and intensity modulated proton therapy (IMPT). Mean dose to hippocampus and subventricular zone were limited to 88.3%,71.5% and 42.3% with IMAT, IMRT and IMPT respectively without disturbance of at least 95% of the prescribed dose in target volume.[18] Brodin et al reported the outcomes of 3 different hippocampal-sparing RT techniques including 3DCRT, IMRT and spot-scanned proton therapy for MB in 17 patients. Mean hippocampal dose and risk of cognitive impairment were statistically significantly decreased with decreasing treatment margin in these 3 different RT techniques. The estimated risk of impaired task efficiency was least by proton therapy regardless of boost margin. IMRT was better than 3DCRT. Due to limited availability of proton therapy, IMRT is an interesting alternative technique at present.[19] However, neurocognitive impairment also correlated with high radiation dose to cerebellum due to interruption in supratentorial connection to frontal region. Hippocampal –sparing RT should be followed up in long-term in both aspects of tumor control and late treatment effects.

Currently there is no clinical evidence of secondary malignancies in MB treated by IMRT which have been reported.

In conclusion, the benefit of IMRT especially sparing of organs at risk in these 3 pediatric cancers is considered to be more significant for treatment outcomes than increased risk of secondary malignancies in current practice. However, it should be used with caution especially in the patients with long term survival. Additional follow up is required for each clinical report in this review article to assess this detrimental effect in pediatric patients.

REFERENCES

1. Brenner DJ, Curtis RE, Hall EJ, Ron E. Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. Cancer. 2000 Jan 15;88(2):398-406.
2. Hall EJ, Wuu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. Int J Radiat Oncol Biol Phys. 2003 May 1;56(1):83-8.
3. Hall EJ. Intensity-modulated radiation therapy, protons, and the risk of second cancers. Int J Radiat Oncol Biol Phys. 2006 May 1;65(1):1-7.
4. Kry SF. Salehpour M, Followill DS, Stovall M, Kuban DA, White RA, Rosen II. The calculated risk of fatal secondary malignancies from intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys. 2005 Jul 15;62(4): 1195-203.
5. Pai Panandiker AS, Beltran C, Billups CA, McGregor LM, Furman WL, Davidoff AM. Intensity modulated radiation therapy provides excellent local control in high-risk abdominal neuroblastoma. Pediatr Blood Cancer. 2013 May;60(5):761-5.
6. Paulino AC, Ferenci MS, Chiang KY, Nowlan AW, Marcus RB Jr.Comparison of conventional to intensity modulated radiation therapy for abdominal neuroblastoma. Pediatr Blood Cancer. 2006 Jun;46(7):739-44.
7. Lin C, Donaldson SS, Meza JL, Anderson JR, Lyden ER, Brown CK, et al. Effect of radiotherapy techniques (IMRT vs. 3D-CRT) on outcome in patients with intermediate-risk rhabdomyosarcoma enrolled in COG D9803--a report from the Children's Oncology Group. Int J Radiat Oncol Biol Phys. 2012 Apr 1;82(5):1764-70.
8. Yang JC, Wexler LH, Meyers PA, Wolden SL. Parameningeal rhabdomyosarcoma: outcomes and opportunities. Int J Radiat Oncol Biol Phys. 2013 Jan 1;85(1):e61-6.
9. Yang JC, Dharmarajan KV, Wexler LH, La Quaglia MP, Happersett L, Wolden SL. Intensity modulated radiation therapy with dose painting to treat rhabdomyosarcoma. Int J Radiat Oncol Biol Phys. 2012 Nov 1;84(3):e371-7.
10. Parker W, Filion E, Roberge D, Freeman CR. Intensity-modulated radiotherapy for craniospinal irradiation: target volume considerations, dose constraints, and competing risks. Int J Radiat Oncol Biol Phys. 2007 Sep 1;69(1):251-7.
11. Kusters JM, Louwe RJ, van Kollenburg PG, Kunze-Busch MC, Gidding CE, van Lindert EJ, et al. Optimal normal tissue sparing in craniospinal axis irradiation using IMRT with daily intrafractionally modulated junction(s). Int J Radiat Oncol Biol Phys. 2011 ;81(5):1405-14
12. Huang E, Teh BS, Strother DR, Davis QG, Chiu JK, Lu HH, et al. Intensity-modulated radiation therapy for pediatric medulloblastoma: early report on the reduction of ototoxicity. Int J Radiat Oncol Biol Phys. 2002;52(3):599-605
13. Paulino AC, Lobo M, Teh BS, Okcu MF, South M, Butler EB, et al. Ototoxicity after intensity-modulated radiation therapy and cisplatin-based chemotherapy in children with medulloblastoma. Int J Radiat Oncol Biol Phys. 2010;78 (5):1445-50
14. Paulino AC, Mazloom A, Teh BS, South M, Okcu MF, Su J, et al. Local control after craniospinal irradiation,

intensity-modulated radiotherapy boost, and chemotherapy in childhood medulloblastoma. Cancer. 2011 ;117(3):635-41.
15. Polkinghorn WR, Dunkel IJ, Souweidane MM, Khakoo Y, Lyden DC, Gilheeney SW, et al. Disease control and ototoxicity using intensity-modulated radiation therapy tumor-bed boost for medulloblastoma. Int J Radiat Oncol Biol Phys. 2011 ;81(3):e15-20.
16. Armstrong GT, Jain N, Liu W, Merchant TE, Stovall M, Srivastava DK, et al. Region-specific radiotherapy and neuropsychological outcomes in adult survivors of child hood CNS malignancies. Neuro Oncol. 2010;12(11):1173-86.
17. Redmond KJ, Mahone EM, Horska A. Association between radiation dose to neuronal progenitor cell niches and temporal lobes and performance on neuropsychological testing in children: a prospective study. Neuro Oncol. 2013; 15(3):360-69
18. Blomstrand M, Brodin NP, Munck Af, Rosenschöld P, Vogelius IR, Sánchez Merino G, et al. Estimated clinical benefit of protecting neurogenesis in the developing brain during radiation therapy for pediatric medulloblastoma. Neuro Oncol. 2012 Jul;14(7):882-9.
19. Brodin NP1, Munck AF, Rosenschöld P, Blomstrand M, Kiil-Berthlesen A, Hollensen C, et al. Hippocampal sparing radiotherapy for pediatric medulloblastoma: impact of treatment margins and treatment technique. Neuro Oncol. 2014;16(4):594-602.