A Review of Intensity Modulated Radiation Therapy (IMRT): A Cost Effective, Personalized Form of Radiation Therapy

Radiation therapy (RT) is used to treat approximately 67% of cancer patients in the US, one or more times during the course of their treatment, or about 1 million patients per year (ASTRO fact sheet, 2009).

In the early 1990s, the standard of care was to deliver RT using a set of intersecting beams, each shaped in two dimensions to the contour of the cancer. Called 3-D conformal radiation therapy (3-D CRT), the combination of two dimensionally shaped beams produces a three dimensional high dose region that approximates the shape of the cancer.

In the late 1990s, the use of a more sculpted beam of RT became common: Intensity Modulated Radiation Therapy, or IMRT. Each IMRT beam does more than simply conform to the shape of the cancer in two dimensions. It actually varies the intensity of the RT according to the dimensions of the cancer in three dimensions. A single IMRT beam is composed of many small "beamlets"; each can be a different intensity. Very complicated cancer shapes can be created, with rapid fall-off of dose immediately outside the cancer. IMRT improves the dosimetry of 3-D CRT, and is often compared with 3-D CRT in clinical studies.

Due to the increase in the utilization of IMRT over the last decade, the complexity of IMRT to plan and administer, and because at first, there was limited published clinical data, some have criticized IMRT as expensive medicine with uncertain benefit. This handout provides an overview of recent data related to the clinical effectiveness of IMRT and describes studies that are currently underway so the reader will understand the reasons for increased adoption of IMRT.

The goal of IMRT is to escalate the dose delivered to the target in order to achieve higher local cancer control rates, without a corresponding increase in normal tissue toxicity. The results are sufficiently encouraging to stimulate further clinical development (see Tables 1 & 2). Initial data indicate that cancer control after IMRT is superior to results from 3-D CRT and randomized controlled phase III trials are underway. The beam shaping and variation in dose intensity of IMRT is done specifically for each cancer patient and is "personalized" RT.

CLINICAL RESULTS SINCE THE INTRODUCTION OF IMRT

This handout reports comparisons between 3-D CRT and IMRT in terms of toxicity, quality of life (QOL) and cancer control outcomes for several different cancers, based on both published data and on clinical trial data not yet published. (It takes an average of 6.75 years for a data set to go from treatment to publication—see Figure 1). For each data set described, the dates of the patient treatments are given. Data have not yet been reported for patients treated after 2006. This handout covers the types of cancer treatments for which the most IMRT data exist. There is no study or data set where patients treated with IMRT have a worse outcome than 3-D CRT with respect to tumor control as measured by local control, disease free survival or overall survival. Not reviewed are data for brain, gastrointestinal, gynecological, sarcoma, and other cancer sites for which there are limited studies.

Extensive data are published on the dosimetric and physics advantages of IMRT compared to 3-D CRT (Braaksma, 2003; Luxton, 2004).

Breast Cancer

RT is well established as a treatment for early breast cancer patients. Studies report that RT results in both increased local control of the cancer and increased survival rates. IMRT has had a major role in limiting acute and chronic toxicity and improving the quality of life for women who receive RT (Yang, 2009; Poortmans, 2007; Table 3).

Head & Neck Cancer – Nasopharynx

Nasopharyngeal cancer is endemic in China and Southeast Asia. The standard of care is a combination of chemotherapy and RT (Lu, 2009). The toxicities of RT and concurrent chemotherapy are often severe, causing delays or dose reductions during chemotherapy, interruptions of RT, and diminished QOL for patients. When toxicities force alterations in the planned therapy, this can lead to decreased cancer control. The use of IMRT has substantially decreased these toxicities, and decreased interruptions in planned therapy.

The principle results of studies that looked at IMRT as compared with earlier forms of RT for nasopharyngeal cancer patients showed decreased normal tissue toxicity and improved local control of cancers (Table 8). These results are not likely to be unique to nasopharyngeal cancer patients because the cancer biology, pathology and staging are similar in other cancer sites.

Head & Neck Cancer – Oropharynx

A phase III multicenter trial (PARSPORT) in the United Kingdom compared IMRT to 3-D CRT in the treatment of pharyngeal cancer patients (Nutting et al. 2009). The percentage of 3-D CRT patients experiencing grade 2 or worse xerostomia was 64%, compared with 41% from the IMRT group – a statistically significant difference.

A retrospective study (Clavel, 2009) compared the toxicity and the efficacy of 3-D CRT and IMRT administered to patients who were also receiving chemotherapy for locally advanced cancer of the oropharynx. The results after three years of follow-up give significantly improved overall survival, disease free survival, and locoregional control of the tumor with IMRT (Table 5).

French physicians did a matched pair analysis of head and neck patients treated with IMRT vs. 3-D CRT (Graff et al. 2007). They studied 67 pairs of patients. Using validated QOL questionnaires, they reported statistically significant improvements in QOL for patients treated with IMRT, including less dry mouth, sticky saliva, mouth pain, jaw pain, and swallowing and eating difficulties. Xerostomia greater than grade 2 occurred in 67% of the 3-D CRT patients and in only 12% of the IMRT patients. There were no differences in cancer control outcomes.

Lung Cancer

Several physics and dosimetry studies have compared 3-D CRT and IMRT treatment plans for the treatment of locally advanced lung cancer (i.e. stages III and IV). The resulting dose distributions and dose volume histograms show better sparing of normal tissues with IMRT. The IMRT plans, delivered lower doses to the healthy lung, esophagus, heart, and spinal cord (Christian, 2006; Liu, 2003; Grills, 2003).

Several clinical studies report that higher doses of RT delivered to the cancer result in improved local cancer control (Kong, 2005; Rengan, 2004). Since IMRT makes it possible for physicians to deliver higher doses without causing commensurate levels of toxicity in healthy tissues, future studies may show greater treatment efficacy with IMRT. Current clinical trials are designed to evaluate whether IMRT can deliver higher doses while holding toxicity to acceptable levels. The outcomes that these studies are designed to measure include local cancer control, toxicity, and QOL (Table 3, 4, 5, 8).

Prostate Cancer

The studies reported to date comparing 3-D CRT with IMRT in the treatment of prostate cancer are not controlled trials, but are retrospective comparisons of 2 cohorts of patients treated in different years. Some studies use a "matched pair" form of analysis.

All of these studies concern "early stage" patients. The definition of early stage varies, and involves age, tumor stage, PSA value and Gleason score. Because of these differences, the studies can be somewhat difficult to directly compare. Some also use different criteria for evaluating PSA control as an endpoint.

IMRT in the treatment of prostate cancer is used for two clinical aims: reduction of treatment toxicity and improvement in disease free survival (DFS). In the quest for higher rates of DFS, some centers have used IMRT to escalate the dose to the prostate, delivering doses that would produce unacceptable levels of toxicity using 3-D CRT. Other centers choose to stay with lower doses, and use IMRT only to reduce toxicity. Some level of urinary toxicity from RT to the prostatic urethra, which runs through the center of the prostate, is unavoidable.

Several randomized trials demonstrate that higher doses of 3-D CRT produce a better DFS rate (Goldner, 2009; Zelefsky, 2008). The Fox Chase Cancer Center experience with prostate cancer patients shows a dose response for doses from less than 72 Gy to greater than 76 Gy (Pollack, 2004). IMRT makes it possible to deliver doses that are higher (≥80 Gy), and there is evidence that these higher doses produce even longer DFS, especially in low and intermediate risk patients.

Patients in the Memorial Sloan-Kettering Cancer Center (MSKCC) study (Cahlon, 2008) attained a higher PSA control rate and a much lower rectal toxicity rate than patients in the MD Anderson Cancer Center (MDACC) study (Kuban, 2008). This is due to MSKCC patients having been treated with IMRT, while MDACC patients were treated with 3D-CRT (Table 7).

RTOG sponsored a phase III trial (0126) comparing different RT doses in the treatment of prostate cancer. The study, which opened in March 2002 and closed in August 2008, involved 1,532 patients. The participating institutions chose whether to use 3-D CRT or IMRT based on technical capability. Patients were randomly assigned to the 70.2 Gy or 79.2 Gy dose groups after the RT treatment modality was selected. About one-third of the patients received IMRT. The study is in the follow up period, and will report on toxicity levels, QOL, PSA failure rates, disease free survival, and overall survival.

The current RTOG trial (0415) for early stage prostate cancer patients compares two other treatment regimens: delivery of 70 Gy delivered over 28 fractions as compared with 73.8 Gy delivered over 41 fractions. Again, the choice of 3-D CRT or IMRT is made by each institution, prior to the randomly assigned dose regimen. The outcomes measured are the same as in the previous trial described above.

These two RTOG trials will allow for a comparison of 3-D CRT and IMRT.

Ongoing Clinical Trials

A search of the NCI clinical trials database for IMRT trials, conducted in August 2009, yielded 169 results; 55 were not pertinent or had been withdrawn. Table 1 gives a listing by cancer type and study phase. The 21 phase III trials, which are ongoing, will yield more data on the value of IMRT in the ensuing years.

Specific RTOG trials using IMRT are listed in Table 2.

Conclusions

A key question regarding IMRT is whether IMRT is cost effective. The cost is higher than other forms of RT, mostly due to increased physician and other staff time. The additional time spent in planning and delivering IMRT is now a necessary part of maintaining accuracy.

With time, more of the processes involved in planning and delivering IMRT treatments will be computer controlled, so staff time will decrease. Manufacturers of RT equipment and software have made significant progress in producing tools that make IMRT easier and faster to plan and deliver. As clinicians perform more IMRT, their speed and proficiency has improved. New, faster forms of IMRT are now available, which speed up delivery, and thereby increase the throughput and reduce the cost per patient.

The effectiveness is initially evidenced by better treatment plans designed to deliver more dose to the cancer and less to surrounding healthy tissues. This allows for less normal tissue toxicity, which maintains the patients QOL. Toxicity prevention is cost effective when compared to the cost of administering treatments for such toxicities.

Better cancer control occurs when higher doses of RT or better combinations of RT and chemotherapy are possible. This is supported by data in the treatment of head & neck, lung and prostate cancer. No data set reports worse outcomes for IMRT patients (Table 8).

The broad use of IMRT will lead to more clinical studies and opportunities to demonstrate lower cost and increased effectiveness. IMRT use started in 1994 and 15 years later the data on IMRT is starting to mature. Within 5 years the number of studies involving IMRT treatments and their outcomes will double. IMRT is not a treatment offered only in academic medical centers, but is used daily in community-based cancer care settings around the world.

Figure 1 – Date Timetable in Months

It takes an average of 6.75 years for a data set to go from treatment to publication

Treatment →	Follow Up	Data Analysis	Time to Publication	Overall Time →
24 – 36 months	24 – 36 months	1 – 3 months	12 – 24 months	61 – 99 months (average 81 months or 6.75 years)

Table 1 – Clinical Trials of IMRT from the NCI Clinical Trials Data System as of August 2009

Cancer Site	Phase I	Phase II	Phase III	Total
Breast	2	10	4	16
Head & Neck	5	28	4	37
Head & Neck Nasopharyngeal		5	1	6
Lung	3	4	2	9
Prostate	5	13	9	27
Anal		2		2
Rectal	2			2
Pancreatic		2		2
Glioblastoma	1			1
Brain Mets	4	3		7
Cervical	1	1		2
Sarcoma		2	1	3
Total	**23**	**70**	**21**	**114**

Table 2 – Radiation Therapy Oncology Group (RTOG) Trials Involving IMRT (N=14) as of December 2009

RTOG #	Phase	Cancer Site	Therapy	# Patients	Date Started – Completed
0615	II	Head & Neck Nasopharynx	Chemo + 3-D CRT or IMRT	46	12/06 – 12/09
0522	III	Head & Neck	Accelerated RT or IMRT + chemo +/- C225	942	11/05 – 3/09
0920	III	Head & Neck	Pre op IMRT +/- C225	0 / 700	11/09 –
0538 CALGB	III	Small Cell Lung	RT + chemo 3 RT schema		3/08 –
0126	III	Prostate	70.2 vs 79.2 Gy 3-D CRT or IMRT	1,532	3/02 – 8/08
0415	III	Prostate	70 Gy in 28 fxs vs 73.8 Gy in 41 fxs 3-D CRT or IMRT	1,067	4/06 – 11/09
0521	III	Prostate	72-75.6 Gy 3-D CRT or IMRT	603	12/05 – 8/09
0621	II	Prostate	Post op RT 3-D CRT or IMRT	46 / 76	4/08 –
0622	II	Prostate	Post op 3-D CRT or IMRT + Samarium 153	9 / 76	4/08 –
0529	II	Anal	Dose painted IMRT & chemo	63	12/06 – 3/08
0822	II	Rectum	IMRT & chemo	75	4/08 – 11/09
0630	II	Extremity Sarcomas	Pre op RT 3-D CRT or IMRT +/- chemo	50 / 102	3/08 –
0921	II	Uterus	IMRT + Cisplatin + Bevacizumab	0 / 34	11/09 –
0418	II	Cervix, Uterus	IMRT +/- chemo Post op	48 / 58	3/06 – 10/08

Table 3 – IMRT Clinical Data
Breast Cancer – 4 Studies

Reference	Institution / Country	Years Patient Treated	# of Patients	Therapy	Outcomes	Comments
Barnett, 2009	Cambridge England	4/06-6/07	404 411	2D Wedged Pair vs. IMRT		Randomized study Improved dose distribution Final results pending
Pignol, 2008	Canada	7/03-3/05	161 170	2D RT or IMRT	Moist desquamation 48% 31%	Correlates with pain and QOL
McDonald, 2008	Emory	1/99-12/03	124 121	3DCRT or IMRT	Skin Toxicity 52% 39%	No differences in tumor control or survival Retrospective comparison
Freedman, 2008	Fox Chase Cancer Center	2001-2006	405 399	2D RT or IMRT	Skin Toxicity 75% 52%	Retrospective comparison

Table 4 – IMRT Clinical Data
Nasopharynx Cancer – 5 Studies

Reference	Institution / Country	Years Patient Treated	# of Patients	Therapy	Outcomes	Comments
Pow, 2006	University of Hong Kong	6/00-7/04	21 46	2D RT vs. IMRT	Improved salivary function and QOL scores with IMRT	Stage II
Kam, 2007	Hong Kong	11/01-12/03	28 28	2D RT vs. IMRT	Xerostomia grade ≥ 2 at 1 yr 82% 39%	Better saliva flow rates and QOL with IMRT
Lee, 2009	RTOG	2/03-11/05	68	IMRT + Chemo	92% 2 yr local control	
Tham, 2009	Singapore	2002-2005	195	IMRT +/- Chemo	3% Xerostomia (grade 3) 90% 3 yr local control 94% 3 yr survival	
Wong, 2009	China	6/04-12/05	175	IMRT +/- Chemo	94% local control 87% regional control 87% 3 yr survival	

Table 5 – IMRT Clinical Data
Oropharynx and Other Head and Neck Cancers – 5 Studies

Reference	Institution / Country	Years Patient Treated	# of Patients	Therapy	Outcomes			Comments
Nutting, 2009	United Kingdom Group (Parsport)	2003-2007	47 47	3DCRT vs. IMRT	Xerostomia grade ≥ 2 64% 41% p < .05			Oropharynx
Clavel, 2009	Montreal	1/00-12/07	149 100	3DCRT or IMRT RT + Chemo	3 yr survival 3 yr NED survival 3 yr local control	3DCRT 76% 72% 85%	IMRT 95% 89% 92%	Stage III or IV oropharynx
Lee, 2006	Memorial Cancer Center	9/98-6/04	71 41	3DCRT or IMRT	2 yr. feeding tube Xerostomia grade ≥ 2	3DCRT 21% 64%	IMRT 4% 41%	
van Rij, 2008	Netherlands	1/99-12/03	88 75	3DCRT or IMRT	IMRT QOL better scores			
Graff, 2006	France	1/01-1/05	67 67	3DCRT or IMRT	Xerostomia grade ≥ 2 67% 12%			QOL matched pair analysis

Table 6 – IMRT Clinical Data
Lung Cancer – 1 Study

Reference	Institution	Years Patient Treated	# of Patients	Therapy	Outcomes	Comments
Yom, 2007	MD Anderson	8/02-8/05	222 68	3D CRT + Chemo IMRT + Chemo	Pneumonitis at I year 32% 8%	Stage III, IMRT had larger lung vols.

Table 7 – Prostate Cancer Therapy for Early Stage Disease

Treatment	Author	Center	Year Pub.	# of Patients	Median Follow-Up (Months)	Dose (Gy) / # Fx	Prostate BED [a/ß=1.5] (Gy)	% PSA Relapse	Late Normal Tissue BED [a/ß=3]	% Grade 2 + 3 Chronic Urinary Toxicity	% Grade 2 + 3 Chronic Rectal Toxicity	% Chronic Erectile Dysfunction
3D Conformal Radiotherapy	Kuban, 2008	MD Anderson Cancer Center	2008	151	104	78 / 39	182	22	130	7+3	19+7	ND
High Dose IMRT	Cahlon, 2008	Memorial Sloan-Kettering Cancer Center	2008	478	53	86.4 / 48	190	15	138	13+3	2+1	34
Prostatectomy	Walsh, 1994	Johns Hopkins	1994	995	4	NA	NA	18	NA	8	1	32
Robotic Prostatectomy	Badani, 2007	Henry Ford Hospital	2007	2766	22	NA	NA	16	NA	ND	ND	21

NA = Not Applicable
ND = No Data Reported

Table 8 – IMRT Clinical Value

Cancer Type	Decreased Local Toxicity	Increased Tumor Dose	Increased Local Control	Increased Disease Free Survival
Nasopharynx	Yes	NE	Yes	Yes
Oropharynx	Yes	NE	Yes	Yes
Other Head & Neck	Yes	NE	Yes	NE
Breast	Yes	NE	NE	NE
Lung	Yes	Yes	NE	NE
Prostate	Yes	Yes	Yes	NE

NE = Not Evaluable

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