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INTRAOPERATIC ELECTRON BEAM IRRADIATION IN PANCREATIC CANCER

Christopher G. Willett and Andrew L. Warshaw

Department of Radiation Oncology and the Department of Surgery, Massachusetts General Hospital, Boston, MA.

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1. ABSTRACT

Intraoperative electron beam radiation therapy (IOERT) is a technique in which a single high fraction radiation treatment is administered at the time of surgery. Using IOERT, the total radiation dose delivered to a tumor can be increased since sensitive normal tissues are removed from the radiation field during the surgical proceduce. Furthermore, while the biologic effectiveness of this single fraction is incompletely understood, it is believed to be equivalent to that of a dose at least two times greater given by means of conventional fractionation. IOERT may improve local tumor control in patients with resectable or locally advanced pancreatic cancer. At the Massachusetts General Hospital (MGH), IOERT is being investigated in the management of pancreatic cancer as a boost treatment in combination with external beam radiation, surgery and chemotherapy.

2. INTRODUCTION

In the past 20 years, there has been substantial progress in the experimental and clinical application of IOERT as a treatment modality for head and neck, thoracic, abdominal, and pelvic neoplasms. A framework of knowledge regarding short- and long- term tolerances of normal tissues frequently irradiated with IOERT has been established by canine experiments (1-12). Clinically, numerous investigators have described treatment strategies and experience with IOERT and have explored the potential value and limitations of this modality. More importantly, their efforts have identified disease sites in which IOERT in combination with surgery and external beam radiation therapy (EBRT) may be of potential value. The objective of this article is to describe the radiobiologic basis of IOERT, review technicals aspects of treatment and summarize the experience of this modality for patients with pancreatic cancer.

3. EXPERIMENTAL IOERT STUDIES

The radiation tolerance of most normal tissues to conventional fractionated EBRT is well understood. Because it is always done during surgery, IOERT is given in a single radiation fraction. IOERT doses usually range from 20 to 40 Gy when given alone and from 10 to 20 Gy when given in combination with EBRT. The biologic effectiveness of this single fraction is incompletely understood; however, it is believed to be equivalent to that of a dose at least two times greater given by means of conventional fractionation. Data from canine experiments by Gillette et al indicate that the effectiveness of IOERT may be as high as five times that of an equivalent dose given by means of conventional fractionation in certain normal tissues (6-12). Information about normal tissue tolerance after large single doses (>10 Gy) was first provided by canine experiments at the National Cancer Institute (1-5). A series of experiments were done to evaluate the tolerance of normal retroperitoneal structures including the aorta, vena cava, kidney, ureters, bile duct and retroperitoneal soft tissues. In addition, attempts were made to define the tolerance of surgically manipulated tissues such as vascular and intestinal anastomoses. Animals were irradiated with doses of 20-50 Gy delivered in a single fraction with an 11-MeV electron beam. Dogs were selected as the animal model so that the size of the normal structures would be as close as possible to that in humans. Table 1 outlines the results of the experiments (1-5). To summarize those data, high doses of radiation are poorly tolerated by functioning organ systems, such as the liver and kidney, and by hollow viscus organs, especially those with small diameter (ureter, bile duct, bowel), while the retroperitoneal soft tissues, vessels and bones all appear to tolerate even the highest dose without significant complications.

Additional studies were performed to determine the tolerance of surgically manipulated tissues because of the likelihood that manipulated bowel or blood vessels might often be in the radiation field when IOERT is combined. These studies, as shown in table 2, indicate the feasibility of combining IOERT with extensive surgical resections, although there are areas in which significant toxicity can result (1-5).

Table 1: Normal-tissue tolerance to IORT in dogs. Data from the National Cancer Institute (1-5)

Tissue	Max.Tolerated Dose(Gy)	Tissue Effect
Aorta, Vena Cava	50	Wall Fibrosis at > 30 Gy
Kidney	<20	Atrophy And Fibrosis
Ureter	20	Fibrosis And Stenosis
Bile Duct	<20	Fibrosis And Stenosis
Small Intestine	<20	Ulceration,Fibrosis, And Stenosis at >20 Gy
Colon	15	Ulceration, Fibrosis, And Stenosis At >15 Gy

Table 2: Radiation tolerance of surgically manipulated tissue of dogs to IORT. Data from the National Cancer Institute (1-5)

Tissue	Max. Tolerated Dose(Gy)	Tissue Effect
Aortic anastomosis	20	Fibrosis and stneosis at > 20 Gy, no anastomosis disruption at > 45 Gy
Biliary anastomosis	<20	Anatomotic breakdown at > 20 Gy
Defunctionalized small intestine	45	Fibrosis and stenosis at > 20 Gy, no suture-line breakdown at >45 Gy

Table 3: Tolerance of canine retroperitoneal tissue to IORT/EBRT from Colorado State University (6-12)

Tissue	Endpoint	Estimated Max. Tolerated Dose: IORT + EBRT
Aorta wall, Branch Arteries	Aneurysms, Thromboses, Narrowing	30 Gy IORT, 20 Gy IORT + 50 Gy EBRT
Ureter	Radiographic abnormalities	25 Gy IORT 17.5 Gy IORT + 50 Gy EBRT
Muscle	M. fibers decrease Vessel lesions	20 - 25 Gy IORT + 50 Gy EBRT
Bone	Necrosis	15 - 20 Gy IORT + 50 Gy EBRT

Gillete *et al* have undertaken prospective long-term studies (2-5 years) of the response of normal tissues in a canine model to IOERT, IOERT with fractionated EBRT, and EBRT alone (6-12). Beagles were allocated to one of these three treatment arms: a. IOERT only, with single doses of 15 - 50 Gy; b. IOERT with single doses ranging from 10 - 42.5 Gy, and c. EBRT with 50 Gy given in 2-Gy fractions over 5 weeks; and EBRT alone with 50 Gy given in 2 Gy fractions over 5 weeks or 60, 70, or 80 Gy given in 30 fractions of 2, 2.33, or 2.67 Gy over 6 weeks. These investigators performed detailed clinical, radiologic, physiologic, and pathologic analysis of irradiated aorta, branch arteries, ureter, bone, and peripheral nerves.

The results of these studies, as shown in **table 3**, show that a. the toxicity of combined IOERT and EBRT is predominantly due to the effect of IOERT, not EBRT, on normal tissues; b. IOERT doses of 10-20 Gy, when combined with EBRT, are the maximum tolerable doses for blood vessels, ureter, bone, and peripheral nerve; and c. previous experimental and clinical data have probably underestimated the long-term tolerance of normal tissues to IOERT.

4. TECHNICAL ASPECTS OF IOERT

At the Massachusetts General Hospital (MGH), there is a dedicated IOERT suite within the operating room. This facility simplifies the integration of IOERT with surgery and permits complete operating room capability as well as delivery of IOERT. There is no requirement of a transport process from the operating room to a radiation therapy suite and operating room personnel (anesthesiogists, OR nursing, and surgeons) remain in a familiar working enviroment.

The MGH facility employs the Siemen's ME accelerator which provides electron energies ranging from 6 MeV to 18 MeV. This system utilizes a "soft" dock system in which there is no physical contact between the cone and linear accelerator. In the "soft" dock system, the cone is secured in the patient by a modified Bookwalter retraction system. There is no further movement of the cone in the patient after it has been immobilized. Once the patient is under the radiation therapy machine, geometric alignment of the treatment cone with the gantry head is achieved by a laser alignment system with appropriate couch movement and gantry rotation.

A large variety of applicators of different sizes and geometries are available to tailor the treatment to the individual anatomy and topography of the tumor bed. For treatment of the tumors that are commonly irradiated (rectal cancer with pelvic sidewall or sacral involvement, pancreas, bile duct, gastric bed, and abdominal or pelvic lymph node diseases), round cylinders are available at 6, 7, 8, and 9 centimeters both with no bevel on the edge of the cylinder and with a 15 degree and a 30 degree for each of the nominal cylinder diameters. Small diameter cylinders of 3 and 4 centimeters are sometimes useful but have a more limited application. For treatment of some pancreatic tumors and for intra-abdominal tumors such as gastric carcinoma, retroperitoneal sarcomas and colonic tumors, either rectangular or elliptical applicators should be available. Elliptical applicators of 12 X 9 centimeters and 9 X 7

centimeters have been very helpful and are easier to position than rectangular ones. An applicator called the "squircle" which has one end circular and the other end rectangular simplifies the problem of field abutment in patients who require more than one IOERT field.

At the time of surgery, the tumor volume (tumor bed after resection or unresectable tumor) to be irradiated is defined by the surgeon and radiation oncologist and marking sutures are placed around the perimeter of the lesion. An applicator is then selected that encompasses the tumor bed, usually with a 1 centimeter margin. A margin of at least 1 centimeter is optimal to allow for both dose and tumor variabilities. When visualizing the tumor or tumor bed through the cone, the marking sutures should be readily identified well within the perimeter of the cone, thus ensuring adequate coverage of the the tumor volume.

Although the IOERT cone can often function adequately as a normal tissue retractor to hold sensitive normal structures out of the IOERT field, patient respiration or spontaneous movement of the bowel can allow normal tissues to move under the cone and insinuate themselves inside the intraoperative field. The cone must be observed to confirm that this is not occurring. If there is evidence that bowel or other normal tissues slip into the IOERT field, surgical packing must be used to hold them out of the way. It is important that the packing itself does not itself enter into the field because this will decrease the electron beam penetration resulting in underdosage of a portion of the tumor volume.

There are certain situations where normal tissues cannot be physically moved out of the radiation field. Thus, it is essential that a technique be available for secondary shielding. We have available standard lead sheets, which can be cut to the appropriate shape and an appropriate number used to attenuate 90% of the radiation beam. The lead is covered with saline soaked gauze and placed over the normal tissues. Lead shielding is often essential if abutting IOERT fields are to be used. Other methods for secondary collimation may be employed, but we have found this method to be effective.

IOERT is currently utilized as a component of a comprehensive treatment program of pre- or post-operative external beam irradiation (45 to 54 Gy in 25 to 28 fractions) frequently with concurrent chemotherapy and surgery for a locally advanced malignancy. Because most patients have received a course of full dose external beam irradiation, IOERT doses usually are in the range of 7.5 Gy to 20 Gy. The selection of dose as well as electron energy are dependent on the amount of residual tumor remaining after maximal resection. Guidelines are as follows: resection margin negative but narrow - 7.5 Gy to 10 Gy, margin microscopically positive or res(m)-10 to 12.5 Gy, gross residual-res(g) 2 cm or less in largest diameter-15 Gy, unresected or res(g) of 2 cm or greater - 17.5 to 20 Gy. Doses of 20 Gy or higher are not utilized unless there have been limitations of delivery of external beam irradiation.

5. RESULTS OF CLINICAL STUDIES USING INTRAOPERATIVE RADIATION THERAPY FOR PANCREATIC CANCER

5.1. Locally advanced pancreatic cancer

There have been a number of institutions in Europe, Japan, and the USA that have evaluated IOERT in the treatment of patients with pancreatic cancer. European and Japanese investigators generally have used a large single dose of electron-beam IOERT (20-40 Gy) without EBRT. At the Massachusetts General Hospital (MGH), the Mayo Clinic, and many other American institutions, IOERT has been used as a boost treatment (10-20 Gy), in combination with EBRT and resection, when feasible.

Initial investigations during the 1970s and 1980s examined the feasibility, toxicity, and value of IOERT in patients with locally advanced pancreatic tumors. This subset constitutes 40% of patients with pancreatic cancer (13). Because these patients are unresectable by a Whipple procedure or total pancreatectomy, because of the invasion in the portal or mesenteric vessels, treatment for these patients has usually been limited to combinations of EBRT and chemotherapy. Conventional EBRT for unresectable pancreatic cancer has been shown to improve the median survival when combined with 5-fluorouracil (5-FU) chemotherapy (14). Because of the limited tolerance of normal tissue in the upper abdomen (liver, kidney, spinal cord, and bowel) to EBRT, total doses of only 45-54 Gy, in 25-30 fractions, have usually been given. For an unresectable lesion, this is an inadequate dose of irradiation, and treatment results from both prospective and retrospective studies reflect this, with high rates of tumor progression and poor survival. The Mayo Clinic reported a local failure rate of 72% for 122 patients with unresectable pancreatic cancer treated by 40-60 Gy EBRT (15, 16). In this setting of poor local control by conventional techniques, IOERT is a logical means of increasing the effective radiation dose to the pancreatic tumor, with avoidance of normal-tissue treatment.

In the 1970s and 1980s, the treatment regimen at MGH was a combination of low-dose preoperative irradiation, IOERT, and high-dose postoperative irradiation (17-19). Patients with locally advanced unresectable disease without any evidence of distant metastases (by abdominal computed tomography (CT) scan and laparoscopy) received 10-15 Gy of preoperative irradiation to the pancreas and nodal tissue, to prevent tumor seeding during surgery. The patient was then taken to the operating room, where an exploratory laparotomy was performed to determine if any metastatic disease was present. If metastases were found, the patient was not eligible for the IOERT. If a Whipple resection or total pancreatectomy was possible, this was performed and IOERT was not delivered. If the tumor was thought to be locally unresectable (usually because of tumor adherence or fixation to the portal vein or superior mesenteric vessel), the patient was evaluated for IOERT. Patients were acceptable for the IOERT if an applicator could fully encompass the gross disease detectable at the time of surgery and if there was no

evidence of metastatic disease beyond the regional nodes. Patients were treated with circular applicators measuring 6-9 cm. Electron energies were in the range of 15-23 MeV. This gave a 90% isodose line at the depth of 3.8 - 6.3 cm overall, with the depth chosen to conform to the measured thickness of the tumor mass at the time of exploration.

Patients received approximately 20 Gy in a single fraction calculated at the 90% isodose line. Biliary bypass was performed if biliary obstruction was present or imminent or if the bile duct was in the IOERT field. Gastrojejunostomy was performed if there was a high-risk of gastric-outlet obstruction or if any portion of the duodenum was in the IOERT field. Generally, stomach and large and small bowel were excluded from the radiation field, except for a portion of the C-loop of the duodenum, which was irradiated.

After recovery from the surgery, the patient returned for postoperative irradiation, with an additional dose of 35-39.6 Gy delivered by a four-field technique to the clipped pancreatic tumor. Postoperative irradiation was usually administered in coordination with intravenous (i.v.) 5-FU, delivered at 500 mg/m^2, generally on the first 3 days of postoperative irradiation.

The median survival was 13 months for the first 68 patients completing the entire protocol of preoperative irradiation, IOERT, and postoperative irradiation. For 33 patients with tumors less than 5 cm in greater diameter, the 2-year actuarial survival and IOERT control results were 20% and 56%, respectively, whereas for 35 patients with tumors greater than 5 cm, these results were 3% and 43%, respectively. Because the locoregional control rates were similar for lesions less than and greater than 5 cm, the difference in survivals was likely due to the more rapid development of metastases in patients with lesions greater than 5 cm. Fifty-four of the 68 patients developed distant metastases. Analysis of the site of distant metastasis indicates that intrabdominal failure (liver and peritoneal surfaces) were the most common sites, with 33 patients developing hepatic metastases and 12 patients with peritoneal spread. Local failure as an isolated failure pattern was less common, with only nine of 68 patients failing in this fashion. It appears that abdominal metastasis, predominantly liver, dominates the clinical course of these patients. The most frequent long-term normal-tissue morbidity was duodenal ulceration, which was usually satisfactorily managed by medical means.

Forty of the 68 patients had pain at presentation, requiring analgesics. Twenty-three of these 40 patients remained pain free, without analgesics, until death. The early data from the MGH suggested better local control with the use of misonidazole as a hypoxic cell synthesizer than for an earlier group of patients treated with IOERT but without the use of misonidazole [18]. However, this trend was not supported by follow-up data, which showed no advantage to the use of misonidazole. Median survival without misonidazole (15.7 months) was actually superior to that with misonidazole (12.5 months) (19).

The use of multiagent systemic chemotherapy in an attempt to control occult metastatic disease with pancreatic cancer has been disappointing, with no studies demonstrating significant benefits from the use of chemotherapy alone (20).

Because of the high incidence of hepatic and peritoneal metastases and the poor results with standard chemotherapy, current and future therapeutic efforts now include evaluation of irradiation with new agents (taxol and gemicitabine). In our current phase I/II study, we are combining preoperative irradiation to the pancreas (50.4 Gy) with continous infusion 5-FU and weekly gemcitabine followed by restaging 3-4 weeks after completion of EBRT. If there is no evidence of distant metastases, IOERT to the primary pancreatic lesion will be given. With this approach, we hope to improve locoregional control, as well as reducing the incidence of hepatic and peritoneal metastases.

The other major group studying IOERT in unresectable pancreatic cancer has been the Mayo Clinic (15, 16). These investigators utilized IOERT (20 Gy) first, followed by high-dose postoperative irradiation. Data from their initial studies revealed a highly significant advantage in local control with IOERT and external irradiation, in comparison with external irradiation alone (40-60 Gy). The actuarial local control at 1 year for those who received IORT is 82%, compared with 48% for those who did not, and, at 2 years, it was 66% and 20% respectively (P=0.0005). The significant improvement in local control did not translate into a survival advantage in the IOERT group, because of the high (>50%) incidence of abdominal failure in both groups. Median survival from the day of exploration was 12.6 months in the external-irradiation alone group and 13.4 months in the IOERT group, and the 2-year overall survival was 16.5% and 12% respectively.

The Mayo Clinic investigators have recently reported their results on using full-dose EBRT before IOERT in an effort to improve patient selection for IOERT (21). This sequence allows restaging at 2-2.5 months after initiation of treatment. Of the initial 51 patients enrolled in this treatment schedule, 14 (27%) did not receive IOERT (excluding three patients with recurrent disease and one patient with islet-cell tumor), the actuarial incidence of local control at 1 and 2 years was 86% and 68% respectively. The median survival of 14.9 months in their current series compares favorably with survivals in other IOERT and external-beam series. When compared with 56 patients treated during the same period at the Mayo Clinic with a different treatment sequence (IOERT followed by high-dose EBRT), the median and overall 2- and 5-year survival (calculated from the date of diagnosis) observed in the current series was statistically higher (median, 14.9 months, compared with 10.5 months; 2-year survival, 27%, compared with 6%; and 5-year survival, 7%, compared with 0%).

Survival improvements seen in the high-dose preoperative group of IOERT patients probably reflect altered and improved patients selection, rather than treatment effect. These differences suggest that giving a full component of EBRT with 5-FU before exploration and IOERT may be more appropriate than giving IOERT as an initial component of treatment. The altered sequence did result in 27% of patients not receiving IOERT as additional treatment, because of already documented disease progression.

However, the alteration in treatment sequence did not appear to influence the incidence of abdominal-disease control. Actuarial local control at 1 year appeared to be better in the high-dose preoperative external-irradiation group (85% compared with 65%); however, this difference did not reach statistical significance.

Investigators at the NCI (Bethesda, Maryland), reported results of IOERT in the treatment of patients with unresectable pancreatic carcinoma (22). Thirty-two patients with unresectable Stage III (locally advanced, positive nodes) or IV (visceral or peritoneal metastases) pancreatic carcinoma underwent biliary and gastric bypasses and were randomized to receive either IOERT of 25 Gy and postoperative EBRT of 50Gy to the upper abdomen or postoperative EBRT of 60 Gy without IOERT. Both groups were treated with postoperative 5-FU. Median survival times for patients with Stage III and IV disease were not different between the IOERT and EBRT groups (8 months); however, for those with Stage III disease, median survival time and time to disease progression were superior in the IOERT group. Complications in patients treated at the NCI included late duodenal hemorrhage in three of 16 patients. They had one early death from respiratory failure in their IOERT group.

In 1985, the Radiation Therapy Oncology Group began a study of IOERT plus EBRT for patients with locally unresected, non-metastatic pancreatic cancer (23). Patients were treated with a combination of 20 Gy of IOERT and postoperative EBRT to 50.4 Gy, in combination with i.v. 5-FU (500 mg/m^2/day on the first 3 days of the EBRT). Eighty-six patients were entered on the study through 6/1/88 and analyzed through 4/90. Fifty-one patients were fully analyzable. Median survival time of the 51 patients was 9 months, with an 18-month actuarial survival rate of 9%. Local control could not be adequately evaluated at this multiinstitutional study. Major postoperative complications were not excessive and occurred in 12% of patients. Two patients had major late morbidity leading to death, one from duodenal bleeding and the second from biliary obstruction. Although this study does demonstrate the feasibility of IOERT in a multiinstitutional setting, it does not demonstrate any advantage of IOERT over conventional therapy for this disease.

5.2. Resectable pancreatic cancer

Local recurrence has been reported in 50-90% of patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas (24). Efforts to improve local control have included the use of pre- and postoperative irradiation, with 5-FU. In the Gastrointestinal Tumor Study Group (GITSG), 45 patients were randomized after resection to receive no further treatment or irradiation plus 5-FU (25). A survival advantage was seen with the combined treatment, which had a 2-year survival rate of 42% and a 5-year survival rate of 14%, over the control arm, which had a 2-year survival rate of 15% and a 5-year survival rate of 5%. The GITSG registered 30 additional patients in the treatment group and replicated and confirmed the improved survival (26).

Although overall survival has been improved by the use of EBRT and 5-FU, the incidence of tumor-bed recurrence has been reported to be as high as 60%, despite adjuvant treatment. This rate of failure is likely due to the high incidence of residual microscopic disease at the standard surgical-transection margins and in retroperitoneal soft tissues following pancreaticoduodenectomy and the inadequacy of 40-50 Gy of EBRT in controlling this level of tumor burden (24). Intraoperative radiation therapy to the tumor bed has been used alone or in combination with EBRT to improve local control after pancreaticoduodenectomy.

The NCI has evaluated IOERT in combination with resection (27). In the NCI trial, a total of 32 patients with localized pancreatic cancer underwent definitive surgical resection. Half of the patients were randomized to receive conventional therapy, consisting of no further therapy, if the tumor was confined to the pancreas, or postoperative EBRT (50 Gy), if the tumor invaded beyond the pancreas or nodal disease was present. The other 16 patients received a single 20 Gy fraction of IOERT at the time of surgery, with 9-12 MeV electrons. In analyzing the therapeutic results, operative mortality (9/32 patients) was excluded. With this manipulation, the disease-free survival was increased in the patients receiving IOERT to 20 months, compared with 12 months for the control group, although this did not reach statistical significance. Local control was thought to be superior in the IOERT group, which arm had better than 80% probability for local control at 12 months, as compared with 0% in the control arm. Unpublished follow-up results of the NCI trial indicate that all patients in the control arm have died, whereas approximately 25% of patients treated with IOERT were still surviving in early 1991 (28). Experience in Japan has suggested that the full benefit of IOERT may not be achieved unless it is used in conjunction with conventional doses of EBRT; this approach was not addressed in the NCI trial (29).

More recently, investigators from the M.D. Anderson Hospital have utilized a combination of preoperative external beam irradiation (45-50.4 Gy) and concomitant protracted-infusion 5-FU (300 mg/m^2/day) for patients with potentially resectable pancreatic cancer (30-33). This was followed by pancreaticoduodenectomy and IOERT (10-20 Gy) of the retroperitoneal bed. Based on this group's experience, it appears that IOERT can be performed with pancreaticoduodenectomy with minimal

morbidity and mortality. In their most recent analysis, no patient has developed a local recurrence (33). The median survival of 41 patients treated with this protocol was 19.1 months.

Studies to date indicate that tumor contaminates the margins of conventional resection in at least 40% of "cleanly" resected cases. This can be addressed by wider dissection (Japanese) or by extending the field of intended cure by irradiation. If the latter is chosen (which we favor), doing it postoperatively does not work (as it logically should not), because tumor is disseminated at operation. If only preoperative irradiation is given, it is still inadequate for long-term control. Combinations of preoperative external-beam irradiation and chemotherapy with IOERT are sensible and in trial at several institutions, including ours.

6. PERSPECTIVE

At the MGH, patients with potentially resectable pancreatic cancer as staged by helical CT scan and laparoscopy, are receiving 10 Gy of preoperative irradiation in 5 fractions followed by resection and randomization to IOERT (10 Gy) to the pancreatic bed or no IOERT. Portal vein 5-FU infusion is started perioperatively and continues for 4 weeks. Following this, patients undergo postoperative irradiation (39.6 Gy) to the pancreatic bed combined with infusional 5-FU. Hopefully, this study should determine of the value of IOERT in patients with resectable pancreatic cancer.

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Send correspondence to : Dr Christopher Willett, Department of Radiation Oncology, Massachusetts General Hospital, 55 Fruit Street, Cox Building - LL , Boston MA 02114 Tel: (617)-726-8146, Fax: (617)-726-3603, E-mail willett.christopher@mgh.harvard.edu