Intraoperative Radiation Therapy

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Summary

Intraoperative radiation therapy is a developing technology that is being explored at least 60 centers around the world. It is not a procedure to be undertaken lightly because of high initial start-up costs (shielding, modification/adaptation of machine head, operating table modifications, remote monitoring equipment, etc.). It demands close cooperation between surgeons, physicists, anesthesiologists, radiotherapists, nurses, and other personnel[76]. IORT is not without its complications[77]. Only recently has the ROTG begun to collect data in a prospective fashion for patients treated with IORT. Much investigative work remains to be done, and, at this time, IORT is a modality best suited for facilities that not only have the technological capacity to embark on such a program, but that also can cooperatively collect meaningful data in a prospective fashion and interpret same.

Uniterms: *intraoperative radiation*

Introduction

In many clinical situations a major obstacle to cancer cure by irradiation is an unfavorable therapeutic ratio. This ratio is defined as follows:

$$\text{Therapeutic Ratio} = \frac{\text{Normal Tissue Complication Dose}}{\text{Cancericidal Dose}}$$

This fraction expresses relative radiocurability (without complication) in any given clinical situation. Obviously, if the dose required to produce normal tissue complications is small in comparison to the dose necessary to eradicate a tumor, then the therapeutic ratio will be less than unity, and tumor cure without complication cannot be accomplished. Conversely, if the cancericidal dose is less than the normal tissue complication dose, then cure without complication will be possible. Happily, the therapeutic ratio is greater than one in a number of clinical situations: early stage Hodgkin's disease, most non-melanoma skin cancers, early cancers of vocal cord or intact uterine cervix.

Unfortunately, the therapeutic ratio appears to be less than one in a number of other clinical situations: glioblastoma multiforme, unresectable adenocarcinoma of the pancreas, malignant mesothelioma, and cancer of the biliary tree, to name a few. In such situations radiation oncologists continually strive to improve the therapeutic ratio by various manipulations: fractionation and protraction of radiation dose; the use of radiosensitizers; adjuvants such as chemotherapy, immunotherapy and hyperthermia; rotational therapy; field shaping; use of multiple fields; intracavitary and interstitial placement of radioisotopes; shinking field techniques, and so on. The most successful of these techniques aim at putting the radiaton dose on the disease and sparing adjacent normal tissues from irradiation.

Complications of therapeutic irradiation generally do not come from irradiation of tumors per se; rather, they are the result of irradiation of transit tissues (Figure 1)

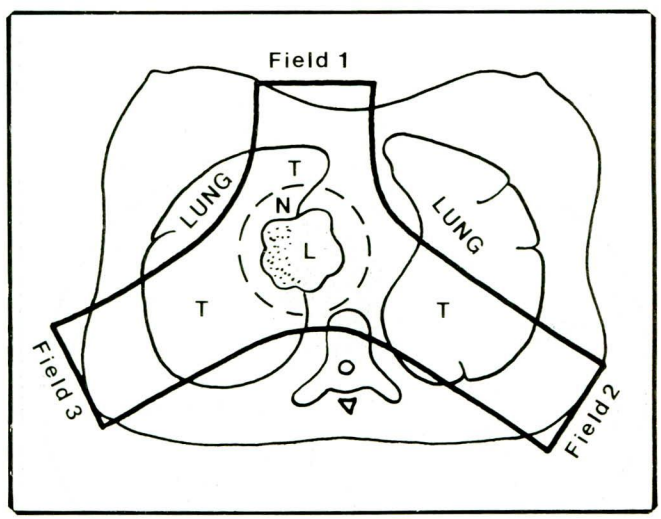

Figure 1 – Schematic of 3-field treatment plan for hilar lesion (L) illustrating pulmonary tissue as matrix tissue (stippled), normal tissue (N) within the target volume (broken line) and transit tissue (T).

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through which the radiation beams must pass in order to reach the tumor. Only uncommonly do radiation complications arise from damage to benign matrix tissues within a tumor. One practical way to deliver the dose of radiation directly to the tumor while avoiding irradiation of anatomically adjacent structures is with intraoperative radiation therapy (IORT). With this combination of surgery and irradiation, one can direct a beam of radiation directly to a surgically exposed unresectable neoplasm or to the bed of a resected tumor (Figure 2). After surgically displacing adjacent critical structures from the path of the beam, one can, by chosing an electron beam of appropriate energy (Figure 3), avoid irradiation of structures deep to the target volume as well. As the volume to be irradiated is relatively small under such circumstances, and as the tissue to be irradiated is largely tumor, not normal tissue, massive doses of the order of 10 to 50Gy can be administered. Yet another advantage of this combination of therapeutic modalities is that surgery is not delayed as it is with preoperative fractionated external beam irradiation.

The disadvantages of IORT are primarily radiobiological and practical. Generally speaking, it is not practical to significantly fractionate or protract a dose of radiation administered through a surgical incision. Consequently, there is no opportunity for malignant cells to redistribute throughout the cell cycle between fractions, nor is there opportunity for hypoxic fractions to be reoxygenated. Additionally, the combination of the two modalities necessitates locating an expensive piece of radiation therapy equipment in a surgical suite, or modifying a radiation therapy room to meet operating room standards, or transporting anesthetized patients

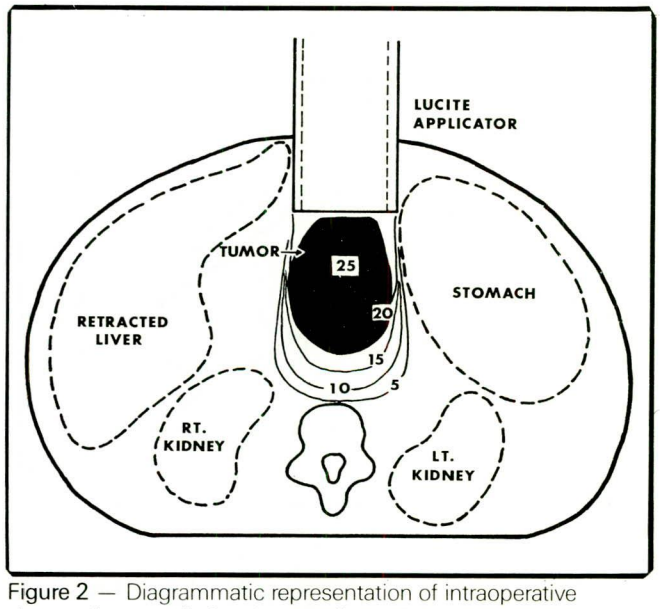

Figure 2 — Diagrammatic representation of intraoperative electron beam radiation therapy directed to an uresectable upper abdominal tumor (shaded area) via a surgical incision. The tumor receives a dose of 20 to 25Gy while the surrounding radioresponsive normal structures receive minimal radiation dose.

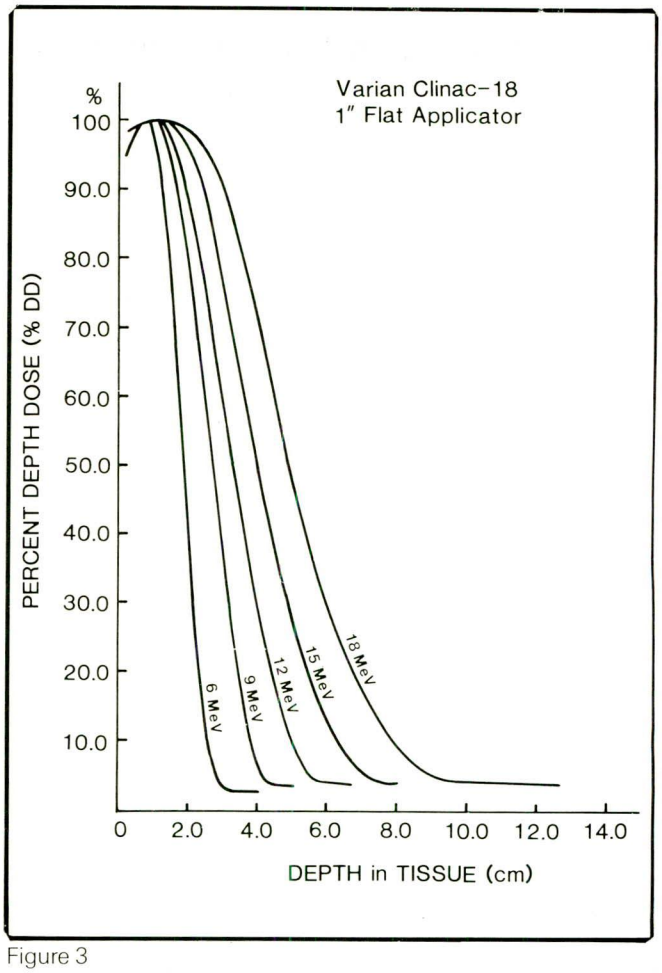

Figure 3

with open surgical wounds from the surgery department to radiation therapy department and vice-versa. Each of these alternatives has its advantages and disadvantages.

Locating a radiation therapy device in an operating room, of course, requires special radiation shielding of floor, walls and ceiling. The cost and/or weight of the shielding and the equipment may be prohibitive, especially if a machine capable of producing megavoltage electron beams is selected. Except in the very busiest of surgical suites, such equipment will be used only infrequently, and even then only a few times a day, probably not frequently enough to economically justify its location.

Modifying a radiation therapy room to comply with accepted operating room standards is neither simple nor inexpensive. Anesthetic gases must be provided, as well as multiple independent vacuum lines. Electrical isolation panels are required as well as improving the room ventilation (25 air changes per hour). Further difficulties attendant to this approach include the circumstances that most existing radiotherapy rooms are actually too small to accommodate major surgical procedures and that anesthesiologists and surgeons may be hesitant to undertake major procedures outside

their normal working environment in the main operating amphitheater.

Problems associated with transporting patients from the main operating room to the radiotherapy department have been extensively discussed elsewhere and may be largely self-evident. Not so obvious, however, is the circumstance that standard anesthesia equipment is not designed to be used while in motion and that processes which proceed predictably while the equipment is stationary (such as volatilization of anesthetic gases) may well become erratic and unpredictable during transport. Furthermore, it is well-known that even relatively minor moving or repositioning of patients with open wounds under anesthesia can produce measureable changes in vital functions. Even though there have been no reported misadventures while transporting patients to and from radiation therapy departments for IORT to date, we feel that such therapy is best carried out in a specially constructed IORT suite where patient transport can be minimized.

History of intraoperative radiation therapy

Beck[1] was the first to use radiation therapy intraoperatively. In 1907 he treated a patient with advanced pyloric cancer and, over the course of the next two years, treated seven additional patients with inoperable gastric and colon cancers by irradiating them directly through abdominal wounds. In 1915 Finsterer[2] reported another series of patients with gastric and colon carcinoma treated in similar fashion. Eloesser[3] used 200 kVp orthovoltage X-rays to treat six patients with advanced gastric and rectal cancers. Bladder cancers were treated intraoperatively by Pack and Livingston[4] and Goin and Hoffman[5]. Their reports appeared in 1940 and 1941, respectively. The Henschkes[6] described "operative irradiation" in 1944 using a scanning technique with contact X-irradiation. Fairchild and Shorter[7] used a 200 kVp orthovoltage beam to irradiate unresectable gastric cancers in 15 patients. During the 1950's Barth[8] and Barth and Meinel[9] used a 150 kVp X-ray beam for intraoperative contact therapy in tumors of the lung, esophagus, and brain. Lutterbeck[10] also treated bladder cancers intraoperatively with direct contact X-irradiation. Before the megavoltage era, intraoperative technique were, in general, applied to advanced, nonresectable neoplasms primarily as a palliative maneuver. In most instances, the long-term results of treatment were not reported.

Abe et al[11,12] pioneered the use of megavoltage beams for IORT beginning in 1964. Initially, a Cobalt-60 beam was employed, but posterior skin reactions from the exit dose prompted the introduction of electron beam therapy. In the subsequent 23 years, Abe has extensively studied the use of intraoperative electron beam therapy in the treatment of many deep-seated malignancies. Results have been particularly encouraging in gastric cancer. As of this writing, approximately 38 facilities in Japan have a capability for IORT.

Goldson et al[13] pioneered the use of IORT in the Unites States in 1975. At Howard University, he and his colleagues constructed a dedicated IORT therapy facility where the entire surgical procedure could be carried out in the same room as the irradiation. By 1983, IORT was being conducted at the Massachusetts General Hospital, the National Cancer Institute, the Mayo Clinic, New England Deaconess Hospital, the Medical College of Ohio and a few other facilities, mainly in the midwest. At present, there are approximately 30 facilities with IORT capability in the United States.

A few European institutions are also exploring IORT as a treatment modality. Fromhold and Glaser[14,15] have treated approximately 25 patients with pancreatic and rectal cancers with IORT combined with external beam irradiation and surgery since 1984. Calvo[16], at the Clínica Universitaria de Navarre in Pamplona, Spain has treated over 200 patients with IORT techniques and DuBois[17] at Montpellier University in France has also treated a few patients with IORT. In China, Huang[18] has treated 153 patients with gastric cancer using intraoperative radiotherapy techniques.

Worldwide interest in this combined modality technique is increasing. Over 300 physicians and scientists from 18 countries attended a two-day symposium dedicated to intraoperative radiation therapy at the Medical College of Ohio in May, 1986. The Radiation Therapy Oncology Group (RTOG) currently has six active protocols aimed at determining the effectiveness of IORT at the following disease sites: stomach (Figure 4), bile duct (Figure 5), pancreas (Figure 6), rectum (Figure 7), uterine cervix (Figure 8) and retroperitoneal sarcoma (Figure 9). A two-day national IORT meeting was held in conjunction with the July, 1987 meeting of the RTOG in Philadelphia. Attending were approximately one hundred physicians and scientists representing a dozen nations. A second international symposium dedicated to IORT is being planned for Innsbruck, Austria, September 11-13, 1988.

Equipment for IORT

The use of superficial and orthovoltage radiation beams for IORT has been largely of historical interest, however, some have found compelling reasons to utilize these modalities even in the megavoltage era. High cost, bulk, and weight are the major disadvantages of megavoltage mechines used for IORT. Superficial or orthovoltage equipment is much less expensive than megavoltage equipment and requires much less shielding. As well, these mechines are easier and less expensive to use and maintain. Major disadvantages of the lower energy beams include low dose rates with resul-

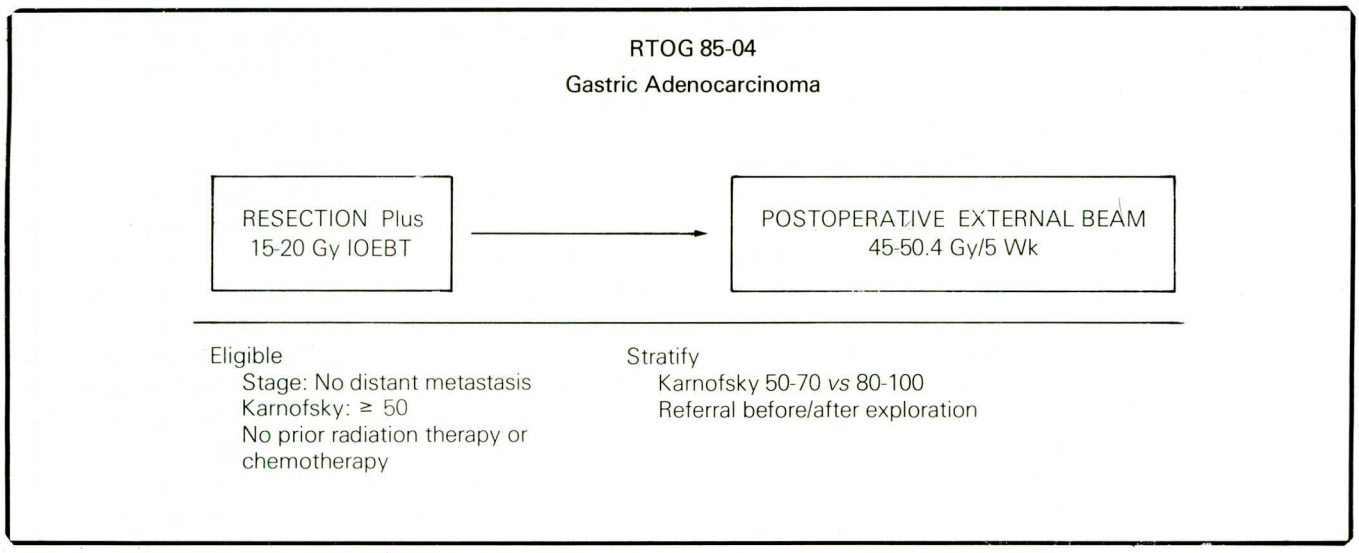

Figure 4 — Schema for RTOG Study 85-04, gastric adenocarcinoma.

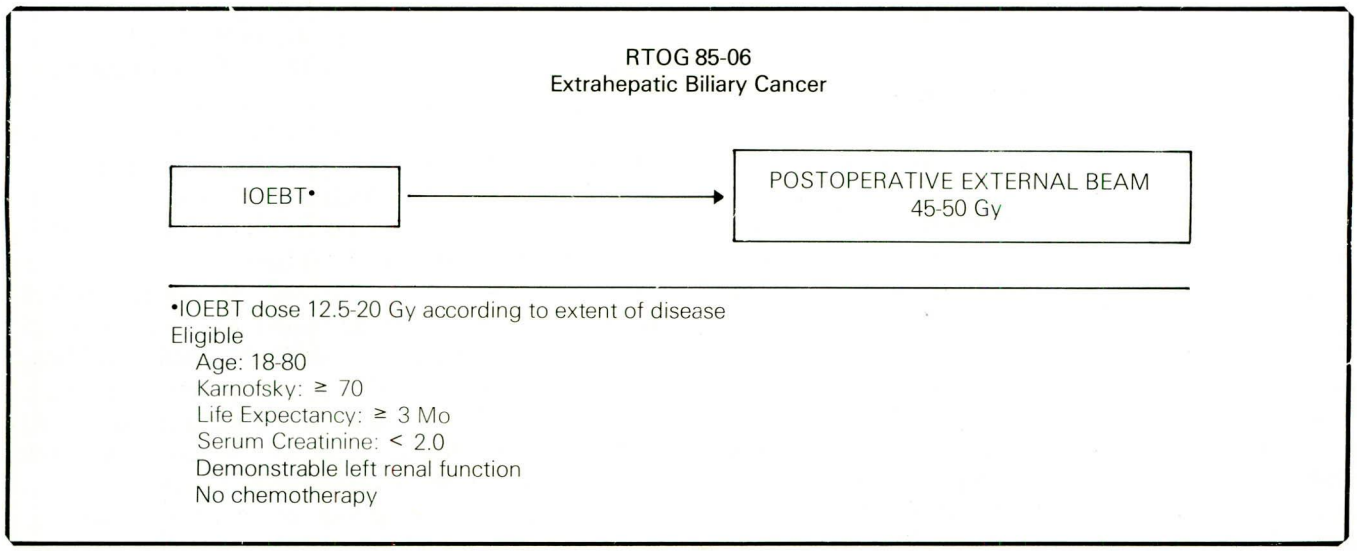

Figure 5 — Schema for RTOG Study 85-06, extrahepatic biliary cancer.

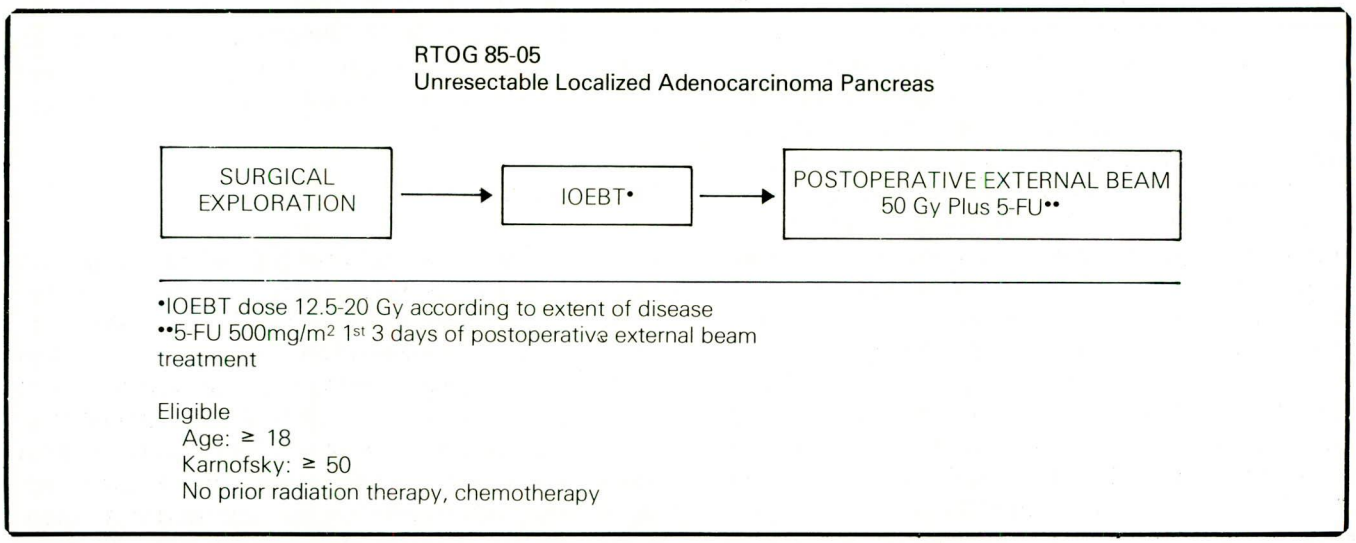

Figure 6 — Schema for RTOG Study 85-05, unresectable localized adenocarcinoma of the pancreas.

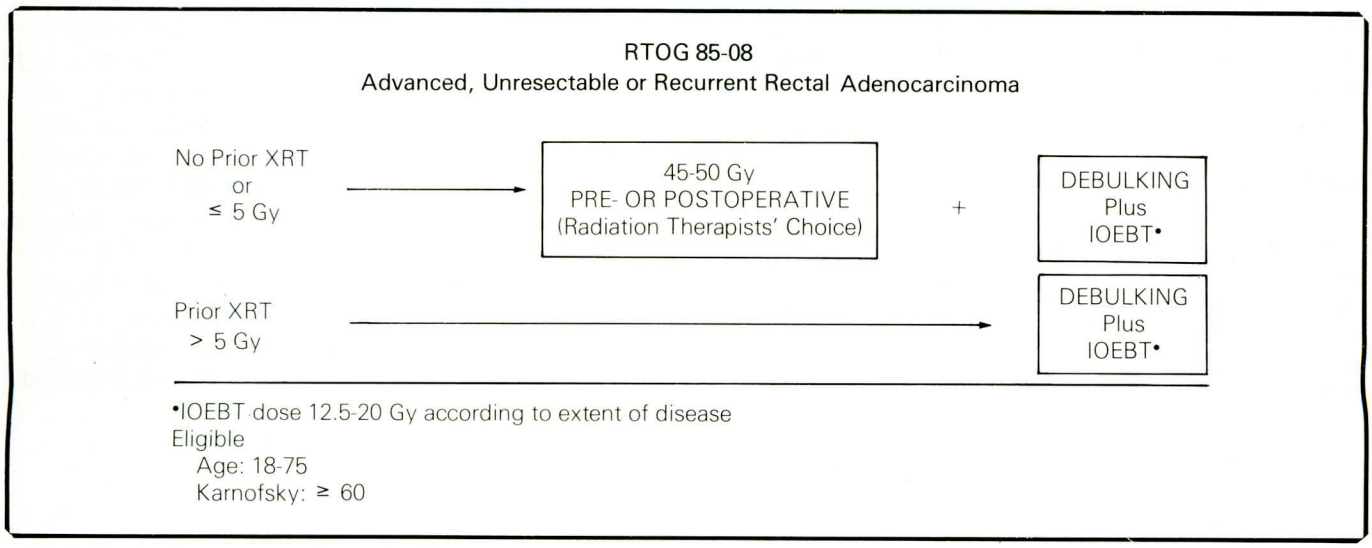

Figure 7 — Schema for RTOG Study 85-08, advanced unresectable or recurrent rectal adenocarcinoma.

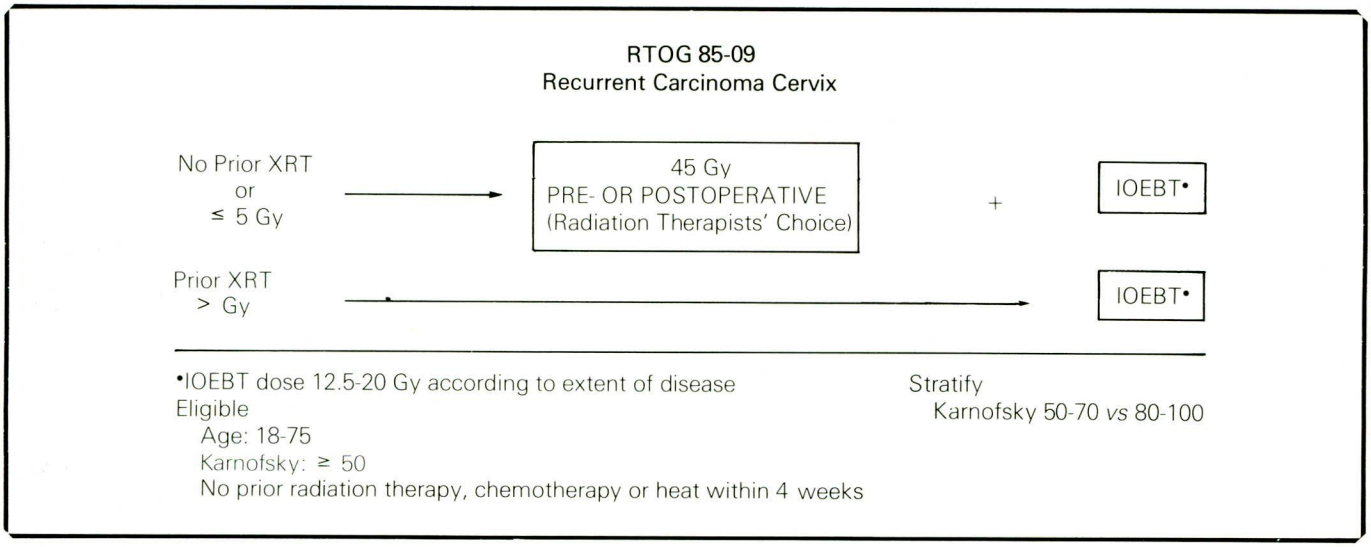

Figure 8 — Schema for RTOG Study 85-09, recurrent carcinoma of uterine cervix.

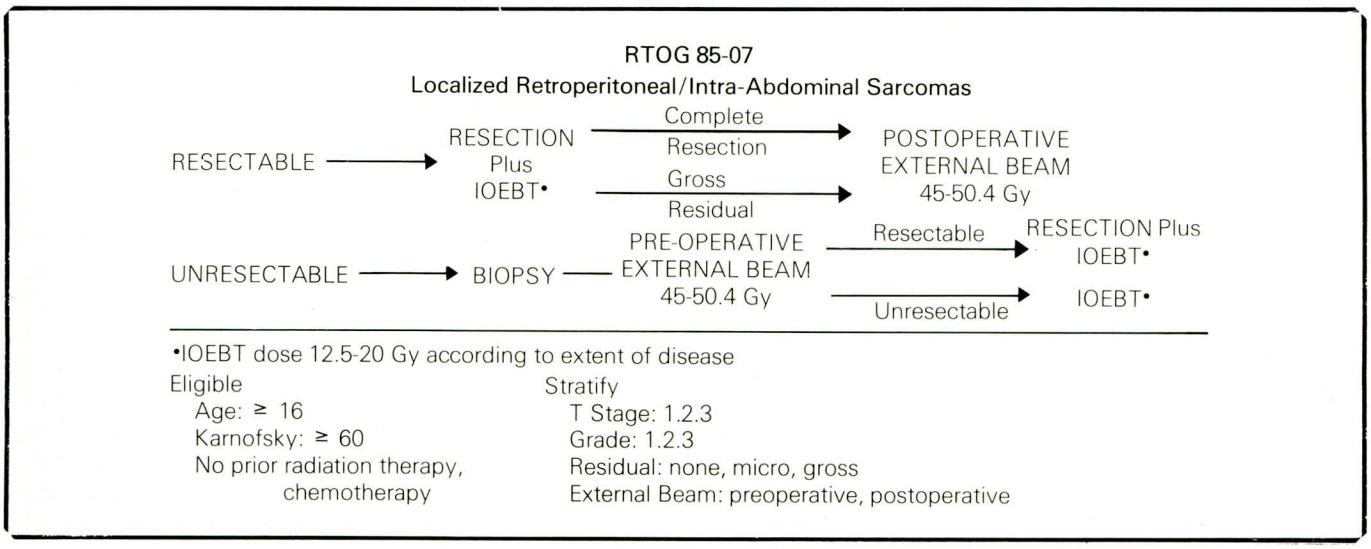

Figure 9 — Schema for RTOG Study 85-07, localized retroperitoneal intra-abdominal sarcomas.

tant longer treatment times, higher exit doses posteriorly, increased bone absorption, and perhaps most importantly, marked dose in homogeneity throughout the target volume.

Superficial X-ray beams for IORT

Krishnamsetty et al[19] treated 35 patients with a superficial X-ray beam intraoperatively at Roswell Park Memorial and while Gilbert[20] has adapted a mobile superficial X-ray therapy unit for IORT.

Orthovoltage X-ray beams for IORT

Orthovoltage X-ray units have been adapted for IORT[21]. The largest experience with orthovoltage IORT is that at the New England Deaconess Hospital where a Phillips 305 X-ray machine was permanently suspended from ceiling tracks in an operating room with a counter-balanced telescopic suspension arm. The unit is operated at 300 kVp and the beam is filtered by 3.2mm tumor, and in one patient who underwent urinary diversion because of a contracted bladder and progressive bilateral hydronephrosis. For T1 cases the one-, three-, and five-year survival rates were 100 percent, 100 percent and 96.3 percent, respectively, and 100 percent, 87.2 percent, and 61.6 percent, respectively, for T2 cases. Heterotopic recurrences were seen in the bladders of 5.3 percent of patients within one year, 9.4 percent in two years, and 19.3 percent in five years. Solitary lesions were controlled in 94.3 percent of patients, and multiple bladder lesions were controlled in 76.9 percent of patients. As expected, the local recurrence rate increased with increasing grade of tumor: 3.6 percent recurrences in Grade I lesions, 6.1 percent recurrents in Grade II lesions and 16.7 percent increase in Grade III lesions. These excellent results appear to be superior to those achieved with other bladder-preserving techniques[64] in terms of local control and patients survival but require confirmation by other investigators.

Sarcomas

At the National Cancer Institute, Kinsella et al[65] evaluated 87 patients with sarcomas for inclusion in a prospective, randomized, controlled IORT study (Figure 21), the first of its kind. Fifty-six patients were found suitable for protocol therapy. Eight refused study, and 48 were randomly assigned to receive either resection and external beam therapy (50 – 55Gy) or resection, moderate dose external beam therapy (35 – 40Gy) and IORT with misonidazole, a radiation sensitizer (3.5Gm/m^2) (Figure 9). Because of patient refusal, ineligibility, the finding of diffuse disease at laparotomy and other factors, 15 patients received IORT and 20 patients received standard therapy. The investigators observed no differences in disease-free survival (20 months) or local recurrence between the two groups of patients, but did observe three patients who developed neuropathy as a result of nerves being included of copper. Between 1982 and 1984, Rich and associates[22] treated 44 patients with orthovoltage IORT. Eighty-five percent of patients had unresectable disease. Tumor sites included pancreas, bile duct, colon, rectum, sarcomas and other tumors. Doses of 12.5 or 17.5Gy were administered. In 18 patients with unresected disease, 78 percent failed locally. Only one local failure was observed in nine patients in whom all gross disease was resected before orthovoltage IORT. One patient developed collapse of the first through third lumbar vertebrae after periaortic orthovoltage IORT. Other complications included ureteric obstruction, pelvic abscess, porta hepatis fibrosis, neuropathy, and small bowel obstruction. This clinical study of the feasibility of orthovoltage IORT continues.

Megavoltage electron beam IORT equipment

Any type of megavoltage radiation therapy equipment capable of generating high energy electron beams can be modified for use in IORT. Betatrons, microtrons, and particularly linear accelerators have been so used. In all cases, it is necessary to construct or purchase special treatment applicators and make provisions for adapting them to the treatment head of the therapy machine. Various such devices have been described[23,24,25,26,27,28]. Figure 10 shows one such device.

Most investigators prefer transparent applicators to facilitate field set-up, however, Abe and others have used metallic circular, rectangular, and pentangular applicators with success. Abe's adapter for the applicators employs a right-angle telescope, as well as a light source (Figure 11). Kinsella and co-workers have developed applicators that are rounded on one side and squared off on the other (so-called "squircels") to facilitate field matching[25]. They have also developed a television system for verification and documentation of treatment fields during intraoperative radiation therapy[29]. Nakamura and Hiraoka[30] have developed a metal pentangular applicator that can be varied in cephalocaudad dimension to accommodate irradiation of the periaortic region in conjunction with the celiac axis in various sized patients.

At the Medical College of Ohio, we have constructed a device to adapt the treatment head of our 18 million volt linear accelerator for IORT (Figure 12). The device is constructed mainly of anodized aluminum and Lucite® . The main assembly (Figure 13) attaches to the treatment head of the linear accelerator with three thumb screws, much as a standard electron applicator

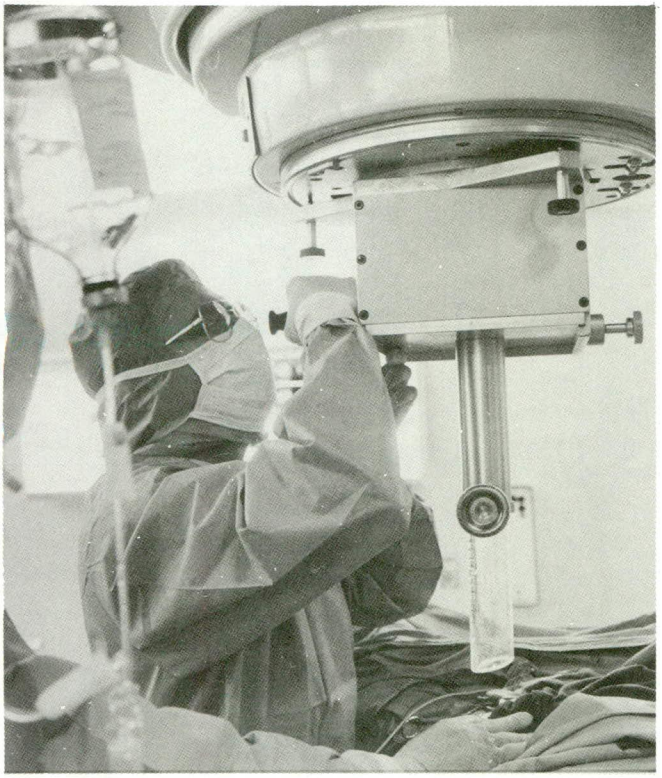

Figure 10 — The treatment head of a Varian Clinac 18 linear accelerator is adapted for IORT with a specially constructed device.

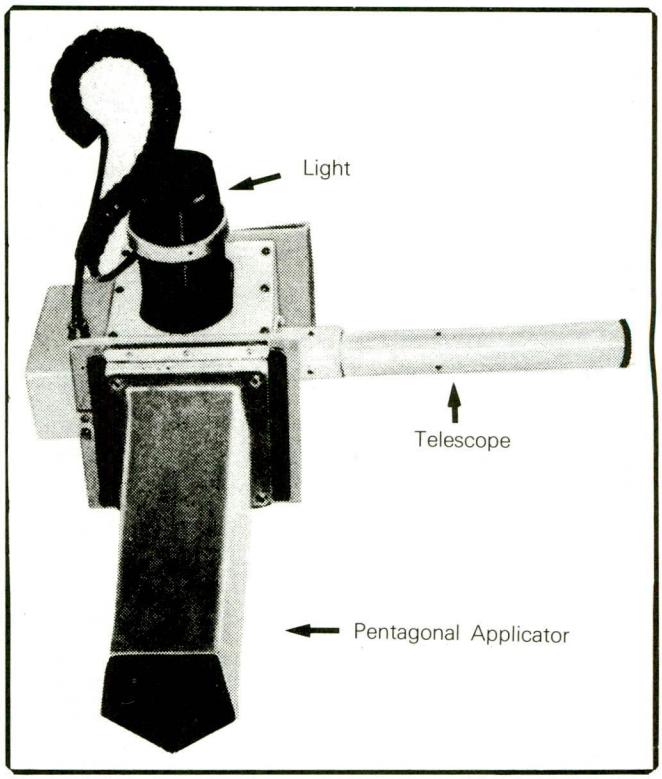

Figure 11 — Kyoto University treatment head adapter with light source, telescope, and pentangular applicator. Modified from Abe[53].

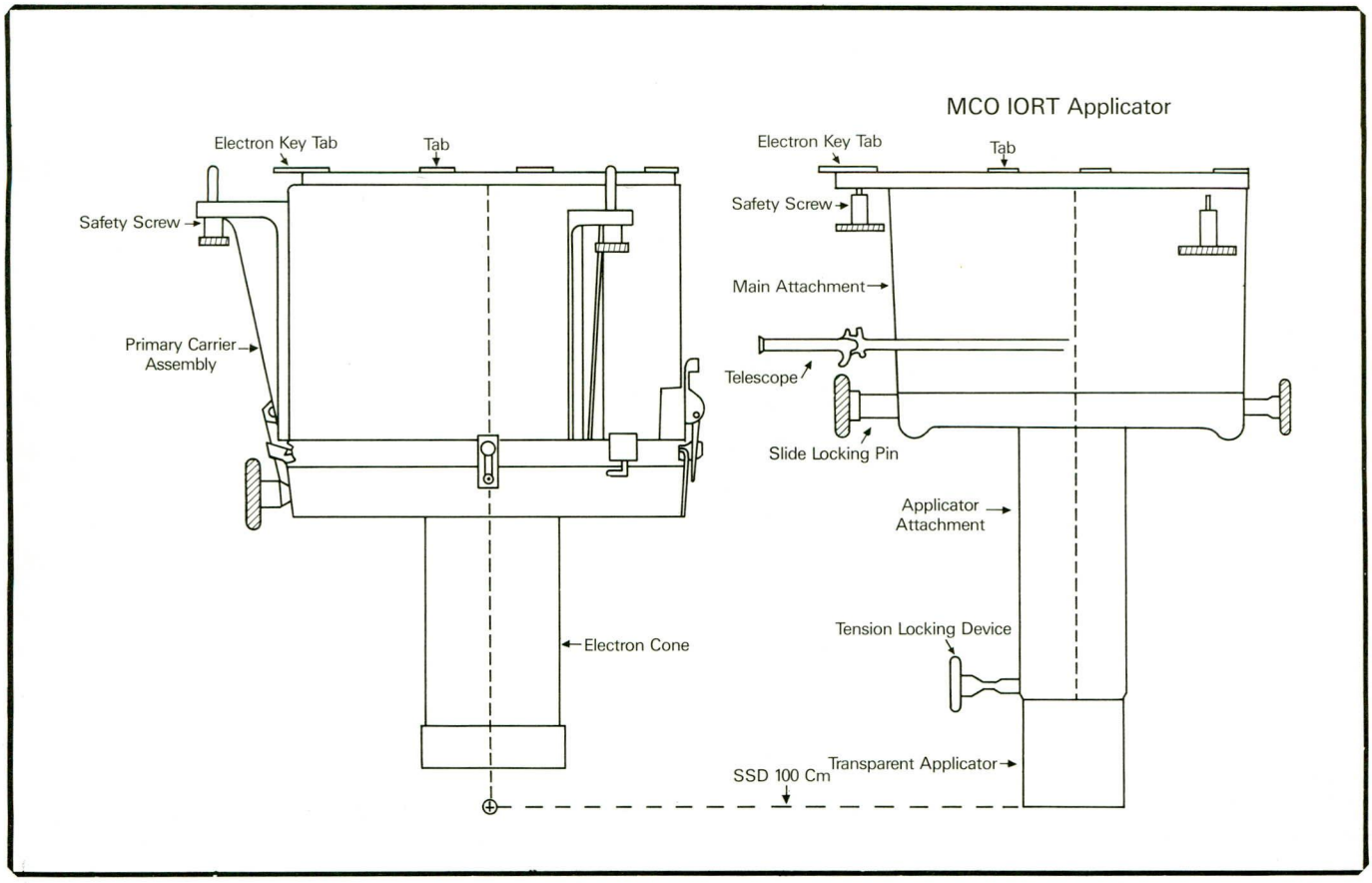

Figure 12 — Two view schematic representation of Medical College of Ohio intraoperative radiation therapy device.

adapter. A right-angle telescope placed at eye level not only permits a "machine's eye" view of the application, but also provides illumination of the field via a built-in fiberoptic light cable. An aluminum baseplate (Figure 14) slides into the bottom of the main attachment and is double-locked in place. Each baseplate is rigidly attached to an aluminum sleeve, into which a Lucite® applicator slides. The applicators (and sleeves) are available in 1/4 inch increments from one to four inches internal diameter.

Graduated etchings on one side of each applicator permit reading of the focus-surface distance at the end of the aluminum sleeve (Figure 15). The ends of the applicators are rounded so as to be relatively atraumatic. The ends of the applicators are either flat or beveled to 15° or 30°. The Lucite® applicators can be locked in the sleeve by slightly turning the knob at the end of each aluminum sleeve. The sleeves, baseplates and main attachment are steam-sterilized while the Lucite® applicators, the right-angle telescope, and the fiberoptic light cable are cold-gas-sterilized.

Once the tumor or tumor bed has been adequately exposed and excellent hemostatis has been obtained, we find it preferable to position the patient under the head of the linear accelerator with the IORT device in place and then slide the applicator out of the sleeve to achieve the desired application (Figures 16, 17) rather than to attempt to "dock" the applicator to the linear accelerator. Docking procedures, used at many institutions, must be done very carefully, as the patient is actually impaled upon the applicator through the surgical wound. The applicator is in contact with delicate internal structures so that even minor movements of the linear accelerator gantry or the table could produce serious injury. It is our procedural policy that under no cir-

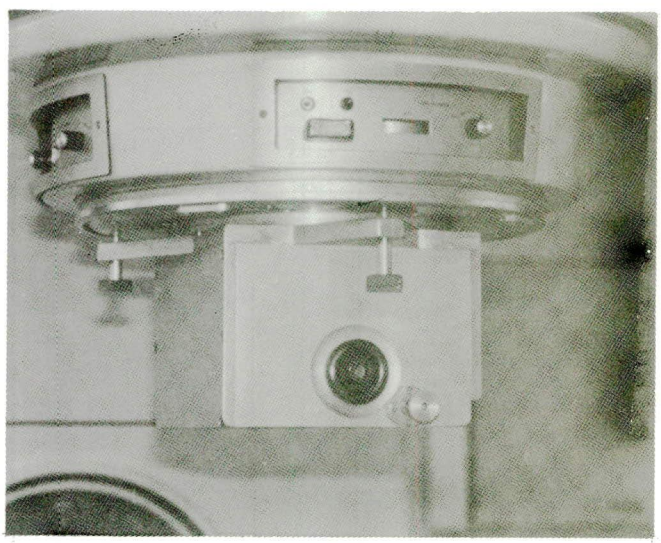

Figure 13 — The main attachment of the Medical College of Ohio intraoperative radiation therapy device attached to the head of a Varian Clinac 18 accelerator with thumb screws.

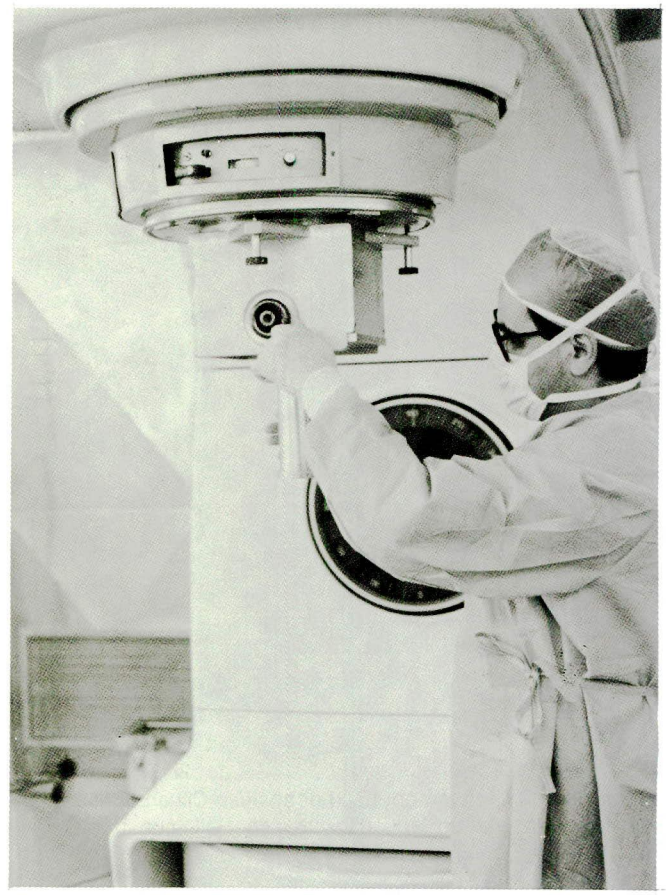

Figure 14 — Aluminum baseplate with attached aluminum cylinder slides into slots in main attachment of Medical College of Ohio intraoperative radiotherapy device.

Figure 15 — Graduated etchings on one side of each applicator permit reading of focus-surface distance at end of aluminum sleeve (See Figures 14, 16 and 17). Applicators are available in ¼" increments from 1" to 4" internal diameter. Applicator ends are either flat or beveled to 15° or 30°. The rounded applicator ends are relatively atraumatic.

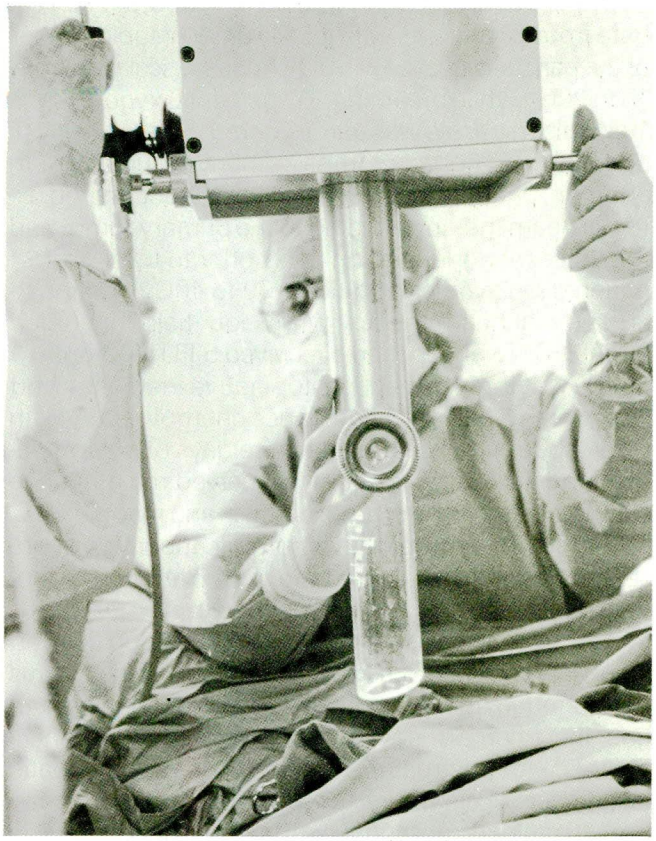

Figure 16 — The lucite applicator slides out of the aluminum sleeve after the patient has been appropriately positioned beneath the linear accelerator.

cumstances shall the gantry or the O.R. table be moved with the applicator tip in contact with the patient.

The need for docking is also obviated by several other IORT systems, including one developed at Rush-Presbyterian-St. Luke's Medical Center in Chicago, which holds the applicator (actually a combination beam-stopper and retractor) rigidly in place by attachment to the side rails of the operating room table. The electron beam is then directed through the applicator to the volume of interest without actually docking the accelerator to the applicator. In order to facilitate accurate beam alignment with the applicator and to insure correct focus-tumor distances, a laser alignment system is being developed commercially.

Even though IORT applicator systems are now commercially available, it is critical that the physical characteristics of the beams exiting the treatment applicator be thoroughly characterized for each conceiveable clinical application before use in patients. The beam output must be measured for each applicator and each electron beam energy at various focus-surface distance settings. One cannot simply assume that inverse square relationships apply, because it is clear that this is not the case[31]. Beam profiles at various depths must also be measured for each applicator as such characteristics will, undoubtedly, be different from those of standard electron beam applicators supplied by radiotherapy machine manufacturers. Radiotherapists cannot be cavalier in these regards.

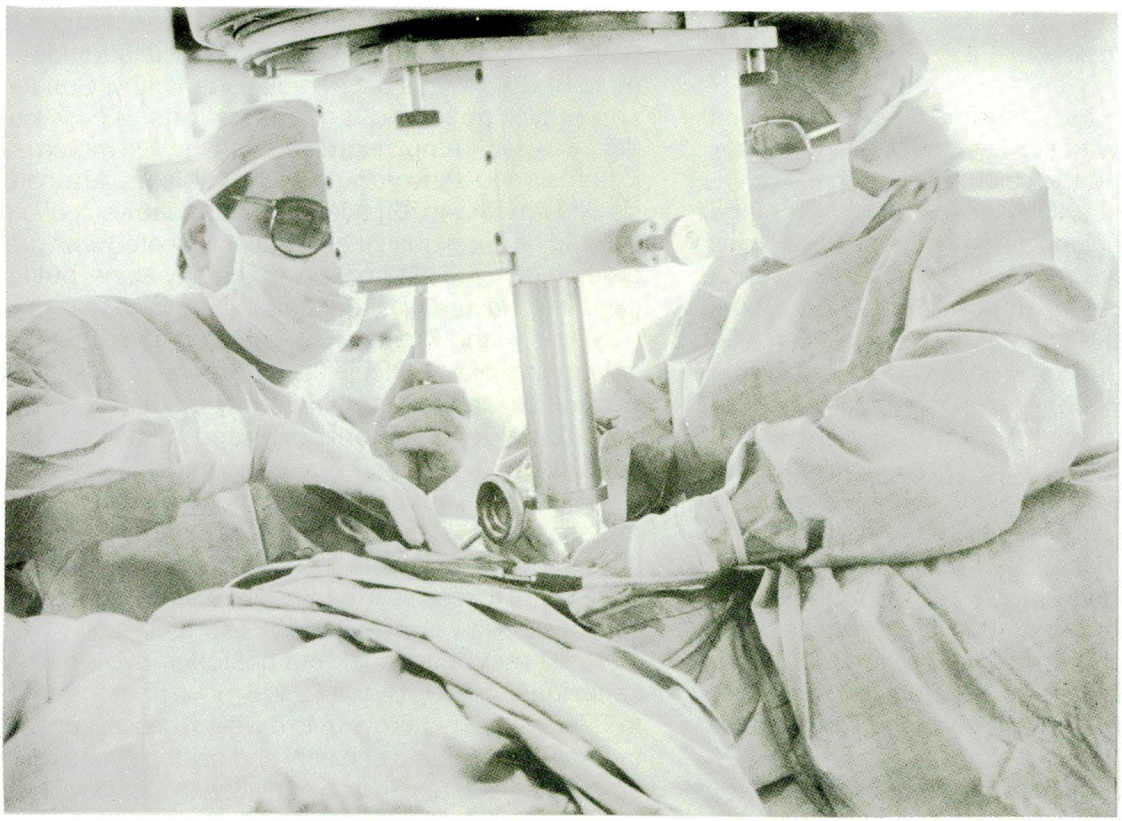

Figure 17 — The lucite applicator slides out of the aluminum cylinder into position through an abdominal wound.

Moving and re-positioning the patient lying on the operating room table with attached anesthetic gear is a clumsy process, not well-suited to the fine movement necessary for accurate positioning for precision irradiation. To circumvent this problem, various modifications of standard operating room tables have been described[25].

Effect of IORT on normal tissues

The effect of large doses of electrons delivered intraoperatively has been studied principally by Tepper et al[32], Sindelar et al[33-36], Kinsella et al[37], Gillette[38] and Hoopes[39]. The radiotolerance of intact organs (or portions thereof) as well as critical anastomoses have been determined in the dog or rabbit as models of the human clinical situation (Table I). Clinical studies[33,34,37] have documented the need to respect the tolerance of certain key structures (ureter, bile duct, intestine, major nerve, etc.) during IORT. The single-dose radiotolerance of tissues in other sites (brain, for instance) has not been completely determined and will require additional investigative effort.

Clinical use of IORT

Fewer than 3000 patients have been treated with IORT worldwide to date. Fewer than 2000 patients have been treated in Japan, and fewer than 1000 in the United States. A wide variety of tumors in many anatomic sites has been treated with this modality.

Cancer of the pancreas

Cancer of the pancreas is the disease that has been most often treated with IORT with at least 320 cases being documented in the scientific literature. For unresectable lesions, the IORT doses employed range from 15 to 50Gy in conjunction with preoperative doses ranging from 0 to 50Gy and postoperative doses up to 50Gy (Table 2). Matsuda[40] reported data from 12 patients with locally unresectable pancreatic cancer treated with 18 to 30Gy IORT followed by 9 to 41Gy delivered by "conformation" external beam therapy. Median patient survival time was 12.5 months. Abe and Takahashi[41] reported data from 100 patients treated at 14 Japanese facilities. Thirty-nine percent of patients received IORT alone plus large field external beam radiotherapy. Only five patients survived more than one year. The average survival time was 5.8 months. The IORT dose ranged from 15 to 40Gy. Eight percent of patients with severe abdominal pain reported relief of same within one week after an IORT dose of more than 20Gy. Thirty percent of patients developed diarrhea, 20 percent bloody stool. Two gastric ulcers and one duodenal ulcer were documented 2 to 40 weeks after IORT.

Shipley et al[42,43] and Wood et al[44] reported clinical data from 29 patients with locally unresectable cancer of the pancreas treated with IORT doses escalating from 15 to 20Gy while breathing 100 percent Oxygen. Since 1982 misonidazole was administered prior to the IORT dose with no apparent improvement in survival[45]. In addition, patients received 10 to 20Gy fractionated external beam therapy directed to the primary tumor and the adjacent node-bearing areas prior to IORT and 27 patients received an additional 30 to 40Gy fractionated external beam therapy with a four-field technique after IORT. Twenty patients received 5-FU (500mg/m^2) on the first three days of postoperative irradiation and 15 patients received maintenance chemotherapy with 5-FU (500mg/m^2) on the first three days of postoperative irradiation and 15 patients received maintenance chemotherapy with 5-FU, doxorubicin and mitomycin-C. Three significant operative complications were observed: A suture line leak at the gastric antrum, a Candida pancreatic abscess, and delayed gastric emptying that required five weeks to resolve. Seventeen delayed complications were observed: Four injuries of the pylorus or duodenum included in the IORT field (one obstruction, three hemorrhage), three cases of retroperitoneal fibrosis with obstruction, and ten cases of pancreatic insufficiency. Pain was relieved or significantly improved in all 16 patients presenting with same. Median survival time was reported as 16.5 months, but as the data matured, this decreased to 13.5 months[46].

Delayed gastric emptying appears to be a common sequel of IORT for pancreas cancer. Goldson[47] was the first to observe this. In a group of 23 pancreatic cancer patients receiving 10 to 20Gy via IORT in addition to 45 to 50Gy external beam radiation therapy, Gunderson et al[48] observed 9 complications: 2 cases of delayed gastric emptying, 2 hemorrhage, 2 symptomatic fibrosis and 3 severe nutritional problems. An analysis performed with 52 patients on study showed patient survival no better than that of patients treated with precision high dose external beam therapy alone, but local in-field failure was reduced to 7 percent[49].

Sindelar and Kinsella[50] conducted a prospective randomized trial of IORT in the management of patients with unresectable Stage III (locally infiltrating tumor with nodal involvement) or Stage IV (visceral or peritoneal metastasis) adenocarcinoma of the pancreas. During 1984 and 1985, 37 patients were evaluated for this study and 27 were found to be eligible. Some refused protocol treatment, and 22 patients were randomly allocated to receive experimental therapy, consisting of surgical biliary and gastric diversion, IORT (25Gy with 18 to 22 meV electrons) and postoperative external beam irradiation (15Gy with 6 to 8 meVp photons in 1.5 to 1.75Gy increments over 5 to 6 weeks) or conventional treatment consisting of biliary and gastric bypass and postoperative external beam radiation therapy to a dose

Table 1 — Maximum tolerable IORT doses: animal studies

Organ	Animal	Maximum tolerance dose (Gy)	Comments
Aorta, intact	Dog	50	Patency and structural integrity preserved; dose-related subintimal and medial fibrosis at ≥ 30 Gy.
Aorta, end-to-end anastomosis	Dog	20	Dose-related fibrosis and stenosis at ≥ 20 Gy, sometimes producing occlusion; no clinical signs of arterial insufficiency and no anastomotic disruption to 45 Gy.
Vena cava, intact	Dog	50	Patency and structural integrity preserved; dose-related fibrosis at ≥ 30 Gy
Small intestine, intact	Dog	< 20	Dose-related mucosal atrophy, mucosal ulceration, muscularis fibrosis, and luminal stenosis at ≥ 20 Gy. Functional small-bowel segments obstruct or perforate at ≥ 30 Gy but defunctionalized bypassed segments maintain structural integrity
Small Intestine closure of defunctionalized intestinal loop	Dog	45	Dose-related fibrosis and stenosis at ≥ 20 Gy no suture line disruption to 45 Gy
Colon, intact	Dog	< 20	Dose-related mucosal atrophy, mucosal ulceration, muscularis fibrosis, and luminal stenosis at 20 Gy. Obstruction can develop at ≥ 20 Gy. Perforation expected at ≥ 40 Gy.
Liver, intact	Rabbit	30	Parenchymal atrophy, fibrosis, necrosis at ≥ 30 Gy.
Bile duct, intact	Dog	20	Dose-related fibrosis and stenosis at ≥ 20 Gy, can lead to biliary cirrhosis
Bile duct, end-to-end at biliary enteric anastomosis	Dog	20	Anastomotic disruption ≥ 20 Gy
Kidney, intact	Dog	< 20	Parenchymal atrophy at ≥ 20 Gy
Ureter, intact	Dog	30	Dose-related fibrosis and stenosis at ≥ 30 Gy can lead to obstructive uropathy
Bladder, intact	Dog	30	Structural integrity preserved; dose-related contraction and ureterovesical narrowing at ≥ 30 Gy.
Bladder, closure cystotomy	Dog	30	Dose-related contraction at ≥ 30 Gy; no suture line disruption to 45 Gy.

Tabela 2 — IORT — Unresectable pancreas cancer

320 patients worldwide	
— Doses	
Preoperative	0 — 50 Gy
IORT	15 — 50 Gy
Postoperative	0 — 50 Gy
— Complications	
Death, 6	
Bleed, Obstruction, Perforation — to 30%	
— Pain Relief 50 — 100%	
— Median Survival 5.8 — 13.5 Months	

of 60Gy in double-split course fashion (20Gy over two weeks x 3). Patients in both IORT and control groups received 5-FU (500mg per square meter) IV daily x 3 concomitant with the external beam radiotherapy and repeated in cycles every four weeks. Ten patients entered the experimental arm and 12 entered the control arm of the study.

Hepatic metastases were observed in ten of the IORT patients and eight of the control group. One early death from respiratory failure occurred in the IORT group. Significant complications of treament were seen in approximately 40 percent of patients in each treatment group. The IORT patients had no acute toxicity, but three de-

veloped late (more than six months) duodenal hemorrhage. Dose-limiting acute radiation enteritis occurred in five patients, late enteritis in three patients. Median survival was 8.7 months in the IORT group, as compared to 8.1 months in the control group. All patients in the control group died within 18 months and in the IORT group with 24 months. The time to disease progression was longer in the IORT group. For patients with local disease only (Stage III) at the beginning of treatment, the time to disease progression and the survival was superior in the IORT group compared to the control group.

IORT has occasionally been used as an adjuvant to surgical resection for cancer of the pancreas. Two of the twenty-six pancreas cancer patients reported by Gunderson et al[48] were treated for gross residual disease after resection. Shipley et al[42] treated four pancreas cancer patients with IORT after radical resection. Hiroaka et al[51] treated the tumor beds (celiac axis, superior mesenteric artery, portal vein, inferior vena cava, aorta, etc.) of 12 patients to 30Gy using 8 meV electrons immediately after pancreaticoduodenectomy. They compared data from this group of 12 patients to that of a comparable group of patients treated with pancreaticoduodenectomy alone. At one year, survival seemed improved in the IORT group, but at two years there was no appreciable difference.

Sindelar and Kinsella[52] conducted the first randomized, prospective, controlled trial of IORT used as an adjunct to surgery in the treatment of resectable cancer of the pancreas. They evaluated 132 patients referred for protocol treatment and found 63 eligible. Seven patients refused protocol therapy, and 56 were randomly allocated to receive surgical resection plus 20Gy IORT with 9 to 12 meV electrons, or surgical resection alone (for disease confined to the pancreas) plus postoperative external beam radiation therapy (50Gy at 1.5 to 1.75Gy per fraction) for lesions extending beyond the pancreatic capsule or with modal involvement. Sixteen of twenty-nine patients randomized to receive IORT were disqualified because of metastatic disease found at surgery, as were 15 of 27 patients allocated to receive routine therapy. Thus, 13 patients were treated with resection and IORT and compared to 12 patients treated with routine treatment.

Five of the thirteen patients on the experimental arm (38 percent) died postoperatively compared to 2 of 12 (17 percent) of patients treated conventionally. Significant complications were observed in approximately half of each group of patients. Between the two groups, no difference was observed in disease-free survival or time to recurrence. When operative deaths were excluded from analysis, the disease-free interval was increased in patients treated with IORT (18.4 months) as compared to the control group (12 months). Survival of the IORT patients tended to be longer than control patients, although statistical significance was not achieved. The local disease control rate was significantly superior in the IORT group. All control group patients failed locally within 12 months compared to 80 percent local control at 12 months in the IORT group.

Given the wide range of IORT doses and the varying combinations of preoperative and postoperative irradiation, it is not surprising that the results of treatment are quite varied. Reported patient survival time ranges from a few months to 13.5 months. Complications have been seen in 10 to 30 percent of patients. Seven treatment-related deaths have been observed. The most common complications reported include gastrointestinal bleeding and/or obstruction, biliary obstruction, peritonitis, perforation of the gut, anastomosis dehiscence, and venous thrombosis.

Interpretation of the rather sketchy available data is confounded by the circumstance that the IORT has been delivered with adjuvant misonidazole, oxygen, 5-FU and other chemotherapeutic agents. The preoperative and postoperative radiation has been also occasionally combined with chemotherapy and even intraperitoneal ^{32}p installation.

One common thread that runs through reports of IORT for unresectable pancreatic is pain relief. This has been observed in 50 to 92 percent of patients presenting with pain and treated with IORT.

Cancer of the stomach

Abe has repeatedly emphasized that in order to cure gastric cancer the primary tumor must be removed surgically. This is because large doses are required to eradicate large tumors, and, in the upper abdomen, radiation tolerance decreases rapidly with increasing volume of tissue irradiated. He has pointed out that for IORT of inoperable gastric cancer, a large volume dose is required making it impossible to sterilize the tumor in one exposure within the tolerance limits of normal structures supporting or surrounding the tumor. Abe has had more experience with intraoperative radiation therapy for gastric cancer than any other investigator, and, over the course of the last 23 years, he has developed certain criteria for intraoperative radiation treatment for such patients (Table III).

Table 3 — Indications for intraoperative irradiation gastric adenocarcinoma

1. Primary Tumor in Fundus or Antrum
2. Primary Tumor Resected
3. No Peritoneal Metastasis
4. No Liver Metastasis (except direct invasion from primary lesion)
5. All Lymph Node Metastases Encompassed in one IOEBT Field

Abe[41,53] has reported clinical results from the treatment of 84 patients whose disease met the criteria listed in Table III. A single dose of 28 to 30Gy was delivered for suspected microscopic foci of residual disease, while 30 to 40Gy was used for gross residual cancer. The pentagonal fields included the lymph node groups around the celiac axis as well as a major portion of the head and body of the pancreas (Figure 18). Abe compared the survival of patients so treated to that of 110 patients treated concurrently by operation alone. Patients admitted to Kyoto University Hospital on Tuesdays received operation alone, while those admitted on Friday also received adjuvant IORT. Although this method of assignment of treatment is open to criticism, the improvement in survival (especially for patients with Stages II through IV gastric cancer) is very encouraging (Table IV). The results for Stage IV disease are particularly impressive as all patients treated with surgery alone were dead by two years, while approximately 15 percent of the patients treated with adjuvant IORT were alive at five-year. It is also noteworthy that three of the five-year survivals came from a group of 19 patients that had incomplete resection of disease at the time of surgery. Abe observed no significant immediate or delayed complications of IORT.

Table 4 — Adjuvant IORT resectable gastric cancer

	Survival	
Stage	Resection	IORT + resection
I	93%	87%
II	62%	84%
III	37%	62%
IV	0%	15%

Abe, Kyoto

Cancer of the Rectum

The American Cancer Society estimates that in the United States approximately 8,500 patients will die of rectal cancer this year[54]. This is a disease in which surgery often fails because of occult residual disease. This is understandable in light of the pelvic anatomy (Figure 19). It is usually possible to get good surgical margins along the bowel, but anteriorly and posteriorly this can be quite difficult because of the intimately related pelvic structures. An adequate posterior margin is often difficult to achieve because of the proximity of the bony sacrum and the presacral neurovascular plexus. In the male, the bladder and the prostate lie just anterior to the rectum and often preclude an adequate anterior margin without extensive debilitating surgery. This is a situation in which IORT has been shown to be effective.

In a joint study, 52 patients with rectal cancer were treated at Massachusetts General Hospital or Mayo

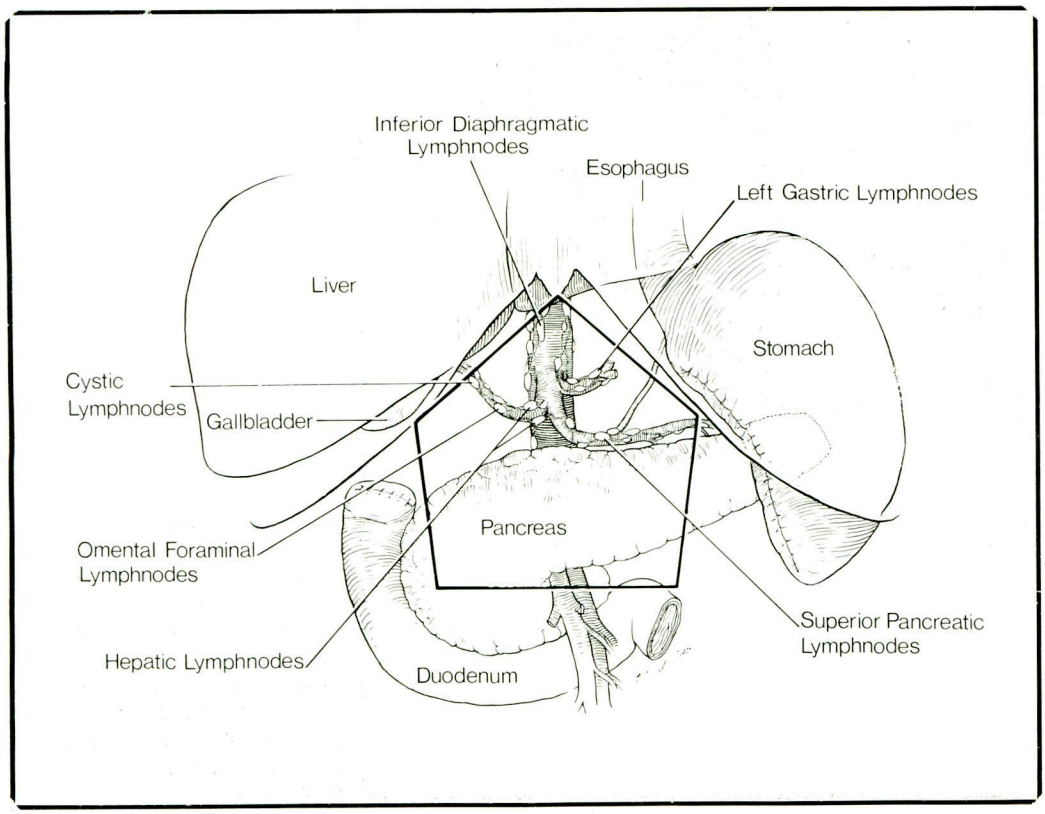

Figure 18 — Pentangular IORT field for irradiation of gastric bed after distal gastrectomy. Modified from Abe[53].

Clinic[55]. These patients received external beam radiation therapy in addition to IORT delivered through the perineal incision of an abdominoperineal procedure. Preoperatively, patients received 50.4Gy external beam radiation therapy at 1.8Gy per fraction. Patients with disease that responded satisfactorily underwent abdominoperineal resection with IORT doses of 10 to 20Gy. For those patients in whom complete resection of gross disease was possible, the local failure rate was reduced to nearly zero and three-year survival rate was nearly double in comparison to historic controls. The expected local failure rate in in such patients without IORT is approximately 50 percent and the expected long term survival without IORT is approximately 30 percent. Obviously, such improvements shown in initial studies deserve confirmation in other centers,

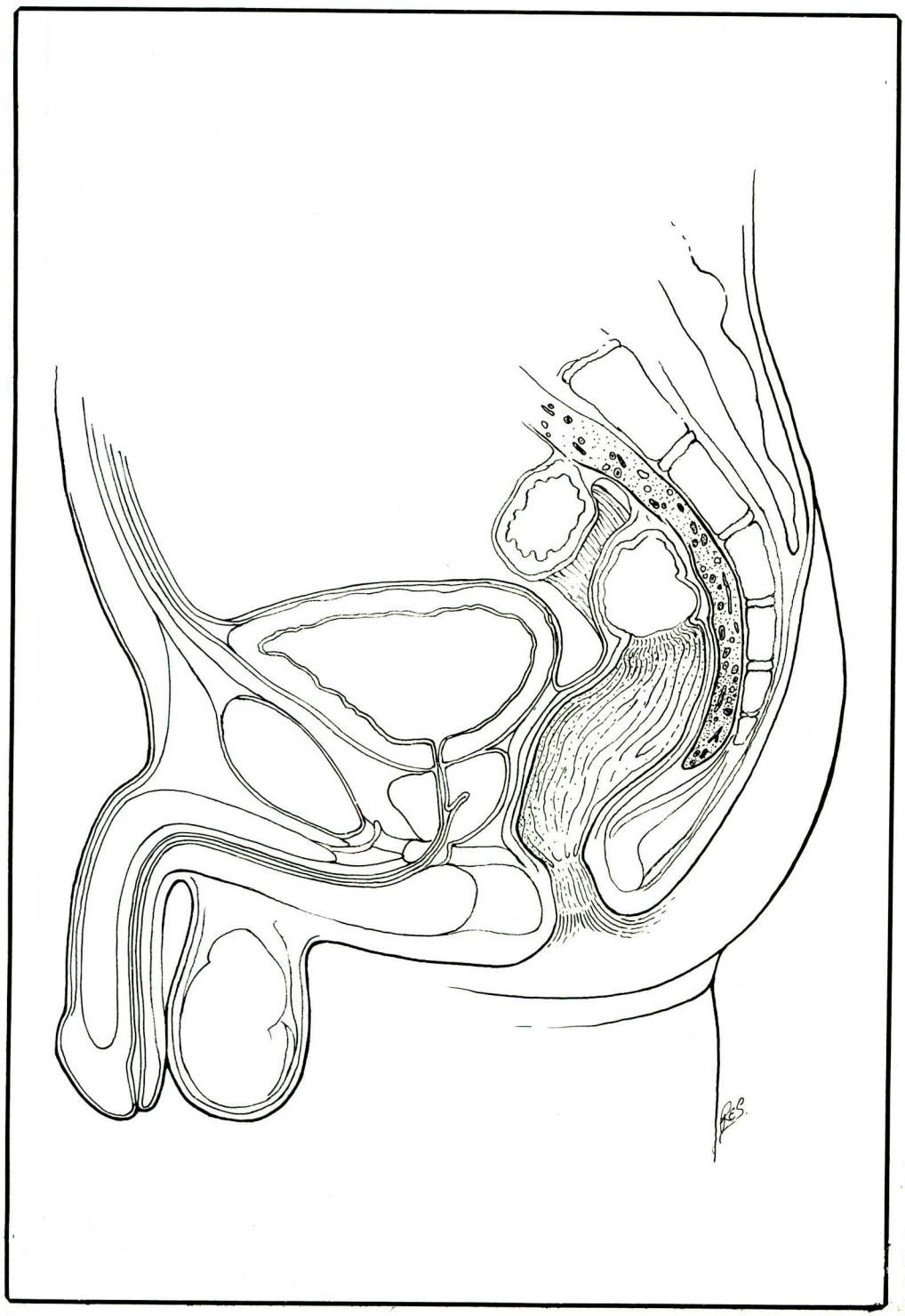

Figure 19 — Sagital view of male pelvic anatomy. It is difficult to obtain adequate surgical margins anteriorly and posteriorly because of the structures intimately related anatomically to the rectum: bladder and prostate anteriorly; presacral neurovascular plexus posteriorly.

or perhaps in a prospective cooperative clinical trial such as the RTOG study (vide supra).

Cancer of the prostate

Takahashi et al[41,56,57] treated 29 patients with prostatic cancer with IORT. Half of their first 14 patients with disease staged A2 through D2 had failed prior treatment (mostly hormonal manipulation) while the other seven patients received IORT as the initial primary treatment. All patients had biopsy-proven disease and all patients were thoroughly evaluated before treatment. The IORT was conducted with the patient in as exaggerated dorsal lithotomy position under general (occasionally spinal) anesthesia through a U-shaped perineal incision (Figure 20). Positioning of the prostate within the treatment applicator was aided with a Young's tractor.

Doses of 20 to 35Gy were administered with 10 to 14 meV electrons. Of patients treated by IORT alone, four who received single doses of 30 to 35Gy achieved local control, but one who received 30Gy had a local recurrence six year after IORT. A single patient treated with 28Gy also failed. A single dose of 20 to 25Gy was delivered intraoperatively to nine patients as a boost dose in conjunction with 50Gy external beam therapy with 10 meVp X-rays at 1.8 to 2Gy per fraction and all nine achieved local control. No serious complications were observed in bladder, urethra, or rectum. The authors suggested that 33Gy delivered by IORT alone, or 25Gy as a boost in conjunction with 50Gy external beam therapy, could be curative for prostatic cancer with minimal morbidity. Clearly additional work must be done to establish the minimal necessary dose of IORT, and the optimal combination of IORT with full-pelvic radiotherapy for prostate cancer. it seems logical that Gleason's

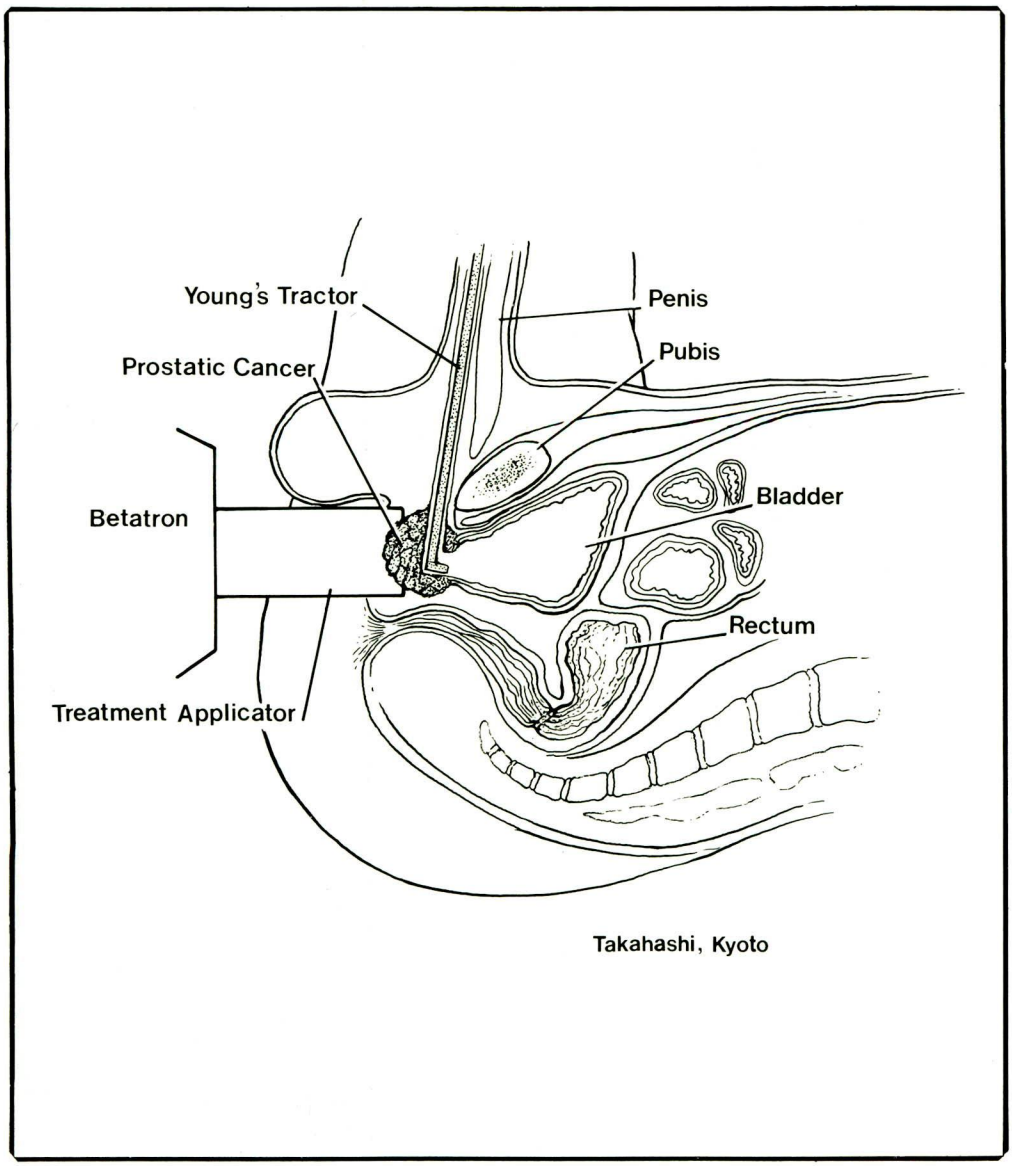

Figure 20 — Diagrammatic representation of IORT for prostate cancer. Modified from Takahashi, et al.[56].

scoring system[58] could be used to aid selection of patients for adjuvant full-pelvic irradiation versus IORT alone.

Cancer of the urinary bladder

Local recurrence of bladder cancer after transurethral resection occurs as often as 80 percent of the time[59,60]. Prophylactic intravesicle installation of chemotherapeutic agents (principally Thiotepa[61] or doxorubicin[62]) have not been completely satisfactory. Matsumoto et al[63] reported clinical results from 116 patients with superficial bladder cancer treated to doses of 25 to 30Gy with 4 to 6 meV electrons followed by 30 to 40Gy whole-bladder external beam irradiation in 15 to 20 days. Normal bladder function was well-preserved except in five patients who underwent total cystectomy because of subsequent multiple recurrences of tumor, and in one patient who underwent urinary diversion because of a contracted bladder and progressive bilateral hydronephrosis. For T1 cases the one-, three-, and five-year survival rates were 100 percent, 100 percent and 96.3 percent, respectively, and 100 percent, 87.2 percent, and 61.6 percent, respectively, for T2 cases. Heterotopic recurrences were seen in the bladders of 5.3 percent of patients within one year, 9.4 percent in two years, and 19.3 percent in five year. Solitary lesions were controlled in 94.3 percent of patients, and multiple bladder lesions were controlled in 76.9 percent of patients. As expected, the local recurrence rate increased with increasing grade of tumor: 3.6 percent recurrences in Grade I lesions, 6.1 percent recurrence in Grade II lesions and 16.7 percent increase in Grade III lesions. These excellent results appear to be superior to those achieved with other bladder-preserving techniques[64] in terms of local control and patient survival but require confirmation by other investigators.

Sarcomas

At the National Cancer Institute, Kinsella et al[65] evaluated 87 patients with sarcomas for inclusion in a prospective, randomized, controlled IORT study (Figure 21), the first of its kind. Fifty-six patients were found suitable for protocol therapy. Eight refused study, and 48 were randomly assigned to receive either resection and external beam therapy (50-55Gy) or resection, moderate dose external beam therapy (35-40Gy) and IORT with misonidazole, a radiation sensitizer (3.5 Gm/m^2) (Figure 9). Because of patient refusal, ineligibility, the finding of diffuse disease at laparotomy and other factors, 15 patients received IORT and 20 patients received standard therapy. The investigators observed no differences in disease-free survival (20 mo) or local recurrence between the two groups of patients, but did observe three patients who developed neuropathy as a result of nerves being included in the IORT field. Seven of twenty patients that received standard treatment developed disabling radiation enteritis as compared to one of 15 receiving IORT. It seems clear that the optimum combination of surgery, IORT, external beam therapy, radiosensitizers and chemotherapy remains elusive as regards the treatment of sarcomas.

Cancer of the Breast

Cancer of the breast is still the most common malignant tumor in the female. Over the past ten years there

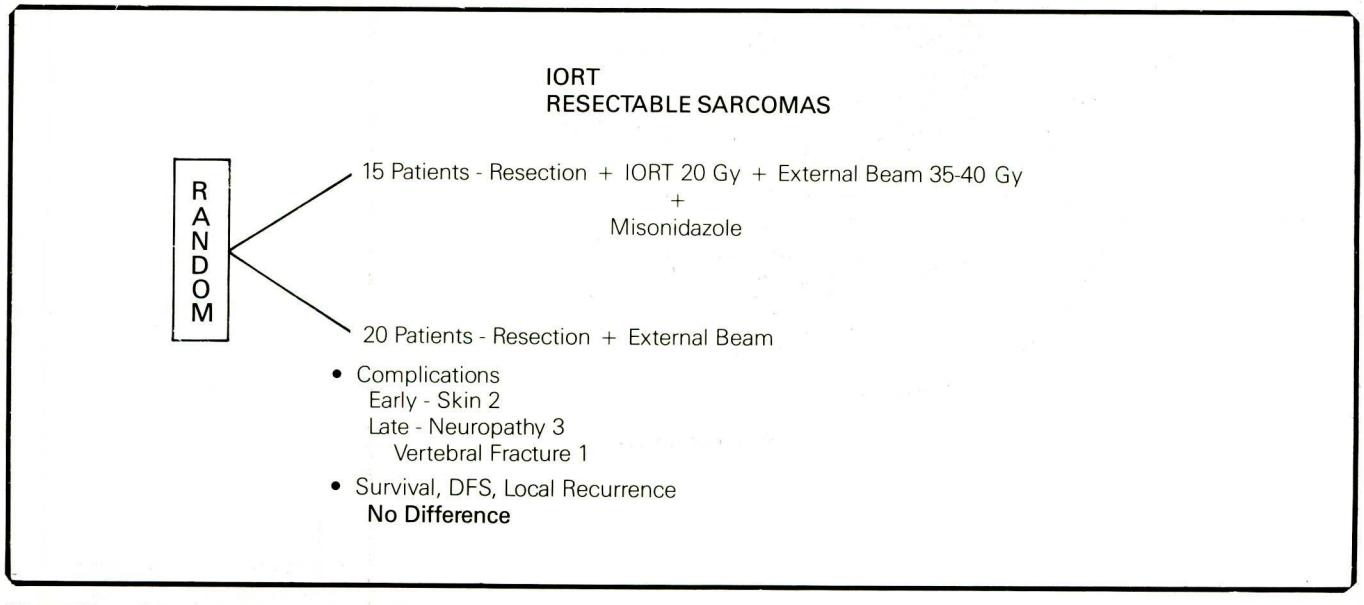

Figure 21 — Schema and results for NCI randomized study of IORT with misonidazole versus conventional treatment for resectable sarcomas. From Kinsella, et al.[65].

has been a growing trend to manage such patients with local excision of the lesion followed by radiation therapy, rather than surgical amputation of the breast. After the breast lump is removed, the breast and adjacent node-bearing regions are treated with external beam radiation therapy; then the dose to the tumor bed is boosted by implantation of radioisotope or by external beam techniques, including electron beam therapy. At the Medical College of Ohio we have begun to employ IORT as the modality for delivering a boost dose to the tumor bed. This is done at the time of axillary node dissection after lumpectomy.

In comparison to standard treatment the procedure described above has several advantages (Figure 22). The patient is spared one hospitalization and one anesthetic for the boost dose. The overall treatment time is shortened, as the radiation boost dose is delivered at the time of axillary node dissection. The overall cost is less because of savings in physicians fees, hospitalization, and in purchase of radioisotope. Radiation exposure to hospital personnel occasioned by radioisotope implant is eliminated. The dose to the skin is minimized because radiation is delivered through the surgical incision. The lung is protected by chosing an appropriate electron energy. As well, one can probably deliver a radiobiologically higher dose to the tumor bed with this procedure, and the chances of a geographic miss are minimized because of direct surgical exposure of the tumor bed at the time of IORT.

We feel that this approach to the definitive radiotherapeutic management of mammary carcinoma deserves further investigation. Obviously, it will require many years to assess the long term effects of such breast conservation treatment.

Brain tumors

The prognosis for patients with malignant brain tumors is dismal. With conventional surgical and radiotherapeutic techniques essentially all patients expire within 18 months. From a radiation therapy point of view, of course, the problem is one of being unable to deliver sufficent dose to the tumor while sparing the surrounding normal brain, the scalp, the skull, etc. Here again, IORT can be employed to enhance the therapeutic ratio.

At the Medical College of Ohio craniotomy is planned and executed in the radiation oncology amphitheater. Recent CT and MRI scans and other studies are used to select the proper position of the head for surgery, plan the procedure and to chose the appropriate electron energy. IORT is employed in conjunction with surgical resection and planned standard preoperative and/or postoperative external beam radiation therapy.

Goldson et al[66] treated 12 patients (10 with astrocytoma, 2 recurrent meningioma) with 15Gy IORT using 9 to 12 meV electron beams in conjunction with 30 to 50Gy conventional external beam irradiation. The patients with meningiomas did well. Three patients with astrocytoma died within 3 months of IORT of causes that may have been related to the IORT.

Abe and Takahashi[41] reported 36 patients with brain tumors treated with IORT doses of 10 to 25Gy in addition to 30 to 40Gy external beam therapy. Survival was generally poor and complications of therapy was not well addressed.

In a pilot study from Tokyo, Matsutani[67] treated 15 patients with glioblastoma multiforme with an aggressive combined modality protocol as follows: 1) surgi-

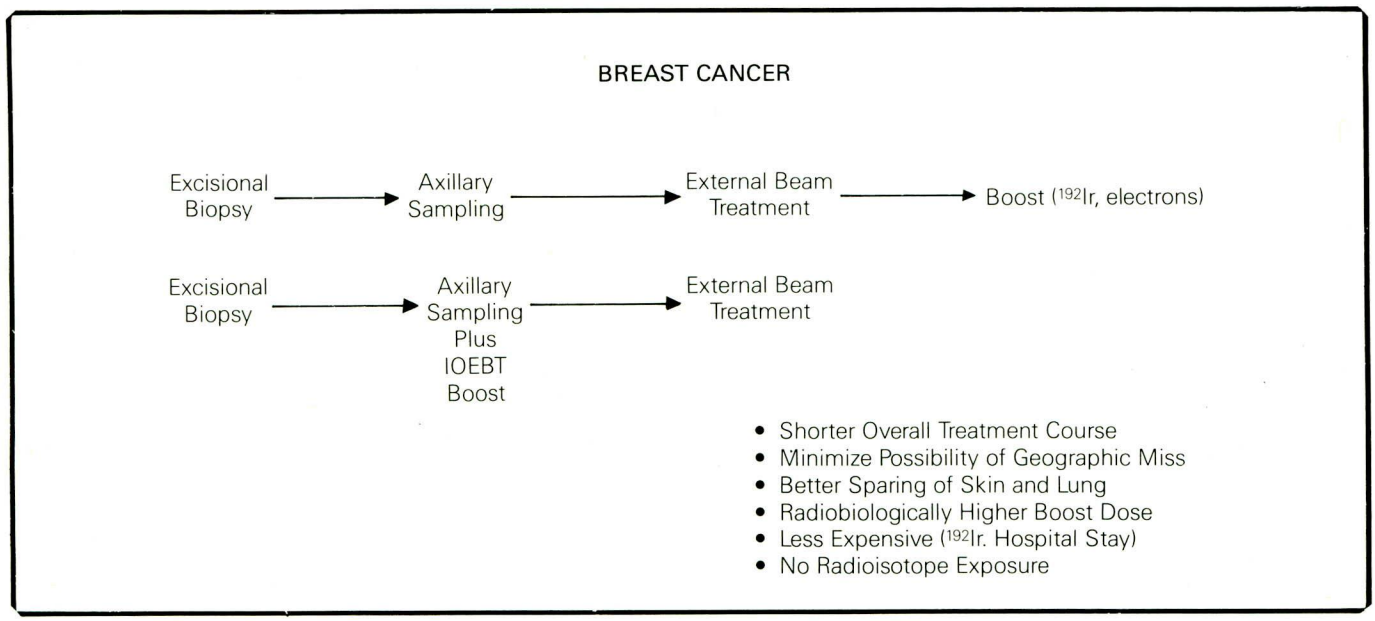

Figure 22 — Comparison of conventional breast conservation treatment with IOEBT.

cal excision of tumor, 2) conventional external beam therapy, 35 to 60Gy, 3) wide re-resection and IORT, 10 to 20Gy with 8 to 20 meV electrons, and 4) additional external beam therapy as necessary to bring the total external beam radiation dose to 60Gy (Figure 23). At the first international symposium on IORT, Matsutani reported a median time of 80 weeks from first operation to tumor progression, as well one- and two-year survival rates of 100 and 62 percent, respectively. Again, these spectacular initial results require confirmation by other investigators.

Cancer of the head and neck

Garrett et al[68] have treated 28 patients suffering from a variety of advanced or recurrent head and neck tumors with IORT in conjunction with external beam radiation therapy. They have employed doses ranging from 10 to 100Gy. The single patient treated with the 100Gy dose had disease involving the mandible and received 60Gy external beam radiation therapy following IORT. Within 2 months a fistula developed and the mandible became exposed requiring resection. Two additional patients died of carotid rupture after IORT doses of 15 to 20Gy in addition to high dose external beam therapy and extensive surgery. Local recurrence of cancer was observed in 13 percent of patients with "close" surgical margins, 25 percent of those with microscopic residual disease and 100 percent of those with gross residual disease, suggesting that IORT with 4 to 11 meV electron beams is an effective treatment for advanced or recurrent head and neck cancer when all gross disease has been resected.

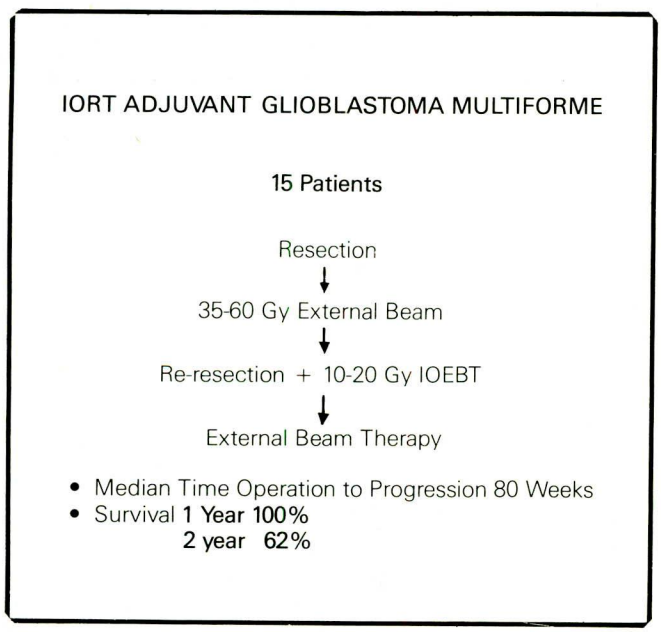

Figure 23 — Schema and results for aggressive protocol employing surgery, IOEBT, and external beam therapy for glioblastoma multiforme. From Matsutani[67].

Other tumors

Intraoperative radiation therapy can be applied to practically any unresectable malignant neoplasm, or to the bed of any tumor where there is a high likelihood of local recurrence. It can be also be used as an alternative to surgical removal in certain situations, such as limited superficial bladder cancers. For other pelvic malignancies, such as carcinoma of the uterine cervix or carcinoma of the ovary, IORT can be used to deliver a boost dose of radiation after standard surgical or radiotherapeutic management, or in patients with recurrent disease who have previously been irradiated to levels of tissue tolerance[69].

The overall survival of patients with cancers of the biliary tree is dismally low and local failure is the rule. Abe and Takahashi[41] reported 27 percent survival at 10.2 months in a group of 59 patients treated with IORT. Gunderson[70] has treated a small group of biliary cancer patients with IORT as a boost treatment in addition to external beam therapy and observad a trend toward increased local control and improved survival in comparison to historical controls.

Surprisingly, few patients with tumors of the chest wall, lung, and mediastinal structures have been treated with IORT[71,72,73]. Initial clinical experience indicates that the radiotolerance of mediastinal structures, specifically the esophagus, must always be respected[73]. These anatomical areas seem a fertile field for further clinical investigation as many tumors of lung, esophagus and mediastinum frequently recur locally.

Certain tumors common to the pediatric group of patients may be eminently suitable for IORT by virtue of the circumstance that irradiation of growing tissues is associated with the risk of serious long term sequellae in terms of local hypoplasia of tissues and organs as well as delayed radiation carcinogenesis. The use of IORT conceivably could reduce these effects by reducing the volume of normal tissues irradiated. Scattered reports of the use of IORT in pediatric tumors [Wilms Tumor[22], retroperitoneal ganglioneuroblastoma and rhabdomyosarcoma[74], and brain tumors[75]] are beginning to appear in the periodic literature. The list of indications and contraindications for IORT is incomplete and will certainly require much additional investigation.

Resumo

A terapêutica por irradiação intra-operatória é uma técnica em processo de desenvolvimento que vem sendo usada em pelo menos 60 centros especializados no mundo. Não é um processo que se inicie sem bases sólidas, porque implica em altos custos (blindagem, modificação e adaptação da mesa e demais elementos de material, equipamento de monitoração à distância, etc.). O

processo exige íntima cooperação entre cirurgiões, físicos, anestesistas, radioterapeutas, enfermeiras, etc.[76]. O IORT não está livre de complicações[77]. Só recentemente o RTOG começou a coletar dados prospectivamente para pacientes tratados com IORT. Há muita pesquisa a ser feita e, no momento, o IORT é uma técnica que só deve ser iniciada quando houver real capacidade para a sua prática e capacidade para coletar dados significativos e operar sua interpretação.

Unitermos: *irradiação intra-operatória*

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