Progress in intraoperative radiation therapy

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From experience with combinations of external-beam and intraoperative radiation therapy in more than 100 patients at the Massachusetts General Hospital and the Mayo Clinic, it is clear that high single boost doses of radiation (1,000 to 2,000 rads) can be delivered safely to the abdominal and pelvic soft tissues during a surgical procedure. It appears that there is no major acute morbidity from this irradiation, although great care must be taken to avoid unnecessary irradiation of hollow viscera or abdominal organs. Preliminary data are very encouraging for the use of intraoperative radiation therapy in addition to external-beam irradiation and surgical resection in locally advanced adenocarcinoma of the rectum. Use of this technique in pancreatic carcinoma and retroperitoneal soft-tissue sarcoma is still being evaluated.

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Instructions to CME enrollees

The multiple-choice examination that appears at the end of this article is designed to test your understanding of the text according to the educational objectives listed below. If you have not registered for this AMA-approved 18-unit category 1 course and wish to enroll, see the test instructions preceding the test.

Educational objectives

Given a closed-book, multiple-choice examination, the enrollee should be able to apply the information learned in the journal article in answering all the test items that require him/her to:

1. Identify advantages of intraoperative radiation therapy as a means of achieving tumor control.

2. Recognize factors influencing the selection of patients to receive intraoperative radiation therapy.

3. Identify technical procedures for the delivery of irradiation intraoperatively.

4. Distinguish the results of studies of intraoperative radiation therapy.

Since the inception of radiation therapy for cancer, the major improvements have been related to the dose distribution between tumor and normal tissue. For most tumor types, the likelihood of local tumor control increases as the amount of radiation delivered to the tumor mass increases. However, in many clinical situations, the dose that can be delivered safely to the tumor volume is limited by nearby or adjacent normal tissue. The development of techniques such as interstitial radiation therapy for head and neck tumors and intracavitary irradiation for cervical tumors has produced high rates of local control for small tumors when combined with external-beam irradiation. Likewise, external-beam radiation techniques have been improved to increase the dose delivered to the tumor mass without increasing the rate of complications referable to irradiation of normal tissue.

The technique of intraoperative radiation therapy is a direct extension of the same concept, ie, delivery of a higher dose to the tumor with acceptable irradiation of normal tissue. Radiation is delivered during surgery from a conventional external-beam machine. The radiation therapist can either move or shield from the path of radiation the normal tissues that otherwise would limit the total dose. The idea of intraoperative radiation therapy is not new. The technique was used in the 1930s by Eloesser[1] and in the 1950s by J. Chesney, MD (personal communication, Miami). The present interest in the technique developed from the pioneering work of Abe and Takahashi[2] in Japan in the 1960s. In the United States, intraoperative radiation therapy programs are active at Howard University,[3] the Massachusetts General Hospital (MGH),[4,5] the National Cancer Institute,[6] the Mayo Clinic,[7] and the New England Deaconess Hospital. This report concerns the overall progress in intraoperative radiation therapy at MGH and the Mayo Clinic.

Patient selection

At MGH and the Mayo Clinic, we are trying to define a subset of patients whose local tumors would be inadequately treated by conventional surgical and radiotherapeutic techniques and who thus might benefit from an increased dose of localized irradiation. Thus, most of our patients receiving intraoperative radiation therapy have locally advanced tu-

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mors where the presence of sensitive normal structures limits the total dose of radiation that we can deliver to the tumor volume. These are generally patients with locally advanced intra-abdominal or pelvic tumors who do not have metastases beyond the regional lymphatics. Our largest group of patients have locally advanced rectal and rectosigmoid tumors. These are patients who present to surgeons with tumors thought to be locally unresectable for cure because of adherence of the tumor to structures such as sacrum, lateral pelvic side wall, or prostate, as demonstrated on physical examination and by pelvic computed tomography. Conventional treatment would consist of high-dose preoperative external-beam irradiation given in the hope of making the tumor resectable. However, even with combined high-dose external-beam irradiation and surgical resection, the local recurrence rate still is very high. In series from MGH,[8] the University of Oregon,[9] and Tufts University,[10] tumors were resectable following preoperative irradiation with 4,500 to 5,000 rads in 50% to 70% of patients but the incidence of local pelvic recurrence was still about 35% to 45% after resection. Thus, intraoperative radiation therapy is being used in this clinical situation as a boost dose to those areas of initial fixation which are at highest risk for local failure.

Adenocarcinoma of the pancreas also is being treated with intraoperative irradiation. The results of conventional surgical treatment are quite poor, the long-term survival rate generally being 5% to 10% in the small subset of patients (about 20% of those who come to laparotomy) in whom surgical resection is feasible.[11] Even in this group, the local failure rate after surgical resection remains quite high, about 50%. However, about half of those patients coming to laparotomy have disease limited to the pancreas and regional lymphatics. It thus appears reasonable in these cases of localized disease to use intraoperative radiation therapy in combination with conventional irradiation techniques to see if local control and cure can be obtained.

A third group of patients in whom intraoperative radiation therapy is being evaluated are those with retroperitoneal soft-tissue sarcoma. This tumor usually is quite large at presentation and difficult to control locally. The long-term survival rate with surgical resection alone is low, about 20%.[12] Both the local control rate and the overall cure rate can be improved by the addition of external-beam radiation therapy. However, serious complications of high-dose irradiation of normal tissue can occur, specifically in the small bowel, and the incidence of local failure can still be appreciable. Thus, intraoperative irradiation of the retroperitoneal tumor bed may be able to decrease both the local failure rate and the incidence of treatment-related complications.

Other locally advanced intra-abdominal tumors can be irradiated during operation if conventional techniques are unlikely to result in a high probability of local control without also causing serious morbidity because of excessive irradiation of normal tissue. Of greatest concern in this regard is the small bowel, but morbidity referable to other tissues, such as the large intestine, stomach, spinal cord, liver, and kidneys, also can result and may be minimized with intraoperative irradiation. A dose of 4,500 to 5,000 rads is near the maximal tolerated dose to stomach, small intestine, and spinal cord and is generally inadequate to produce a high likelihood of tumor control in most clinical situations.

Technical approaches

There have been technical differences in intraoperative radiation therapy as used at the various US institutions. Different machines have been used, various constraints have been imposed by the location of the radiation therapy machine relative to the operating rooms, and there have been philosophical differences regarding the combinations of intraoperative irradiation, conventional radiation therapy, and surgical resection to be used for specific tumor types. The philosophies at MGH and the Mayo Clinic have been fairly similar, favoring a combination of high-dose external-beam irradiation, surgical resection when it can be performed safely, and intraoperative radiation therapy using electron beams.

At MGH, surgery is performed in a regular operating room, with surgical resection of the tumor being carried out as it appears appropriate. If there are no metastases beyond the regional lymph nodes and if a site at high risk for local failure is definable by the surgeon and the radiation therapist, the patient is considered a candidate for intraoperative radiation therapy. Clear plastic (Lucite) cylinders of various sizes are available in the operating room which can be used as retractors to move normal tissue outside the path of the

Preliminary results in 38 patients with rectal or colonic carcinoma are quite encouraging

radiation beam and to confine the beam. The appropriate size is one that encompasses the tumor volume with adequate margins yet allows maximal sparing of normal tissue. Occasionally, additional surgery to obtain optimal exposure of the tumor volume and to minimize irradiation of normal tissue is necessary. For patients who require abdominoperineal resection, decisions are also made in the operating room regarding the use of an abdominal versus a perineal approach and use of a prone versus a supine position for the intraoperative irradiation. After the appropriate cylinder size has been determined, the patient is prepared for transport to the radiation therapy department. The abdomen is temporarily closed with a few stay sutures, and the operative

Table 1. Patients receiving intraoperative radiation therapy at Massachusetts General Hospital, May 1978 to August 1982

Site or type of tumor	Number
Rectum and rectosigmoid	39
Pancreas	21
Sarcoma (chest, abdomen, pelvis)	7
Sarcoma (extremity)	5
Cervix	5
Other colonic, small-bowel tumors	4
Others	4
	85

area is covered with a number of layers of sterile drapes. During transport to the radiation therapy department, with the aid of a patient lift (Surgilift, Trans-Aid Corp, Carson, Calif), portable anesthesia equipment is used. The radiation therapy room will have been prepared so it can function as an operating room, with adequate surgical supplies available. In the radiation therapy department, the patient is moved to a conventional radiation therapy couch and is redraped, the treatment field is re-exposed, and a clear plastic cylinder is inserted to cover the tumor volume. Occasionally, additional packing may be required to hold some normal tissues out of the radiation field, or lead strips used to avoid irradiation of normal structures that cannot be moved out of the beam's path. While the patient is being monitored from outside the room, a large single dose of radiation, generally about 1,500 rads (but varying from 1,000 to 2,000 rads) is delivered to the 90% isodose line. Electrons are used for the irradiation, as the total depth of beam penetration can be adjusted by alteration of the electron energy. Thus, we can minimize the irradiation of deep structures (such as posterior skin surface or spinal cord) and deliver a uniform dose of radiation throughout the tumor volume. After completion of the irradiation, the operation is completed in the radiation therapy department if only simple skin closure is required or in the operating room.

At the Mayo Clinic, exploration or resection or both are performed in a regular operating room and decisions are made regarding indications for intraoperative radiation therapy. Then, reexploration is carried out in one to ten days in

Occasionally, additional surgery is needed to obtain optimal exposure of the tumor volume and to minimize irradiation of normal tissue

an operating room in the radiation therapy department, following which the patient is transferred to the nearby treatment room.

Results

The combined series of patients receiving intraoperative radiation therapy in the United States now totals more than 230: 100+ at Howard University, 85+ at MGH, about 30 at the National Cancer Institute, about 30 at the Mayo Clinic, and 29 at the New England Deaconess Hospital. The first of these patients were treated at Howard University, generally with intraoperative radiation therapy alone[3]; most did not have external-beam irradiation or surgical resection. The Howard University group demonstrated the feasibility of delivering a high single dose of radiation during a surgical procedure without producing serious patient morbidity.

At MGH, patients with locally advanced rectal or colonic carcinoma have been the single largest subset (table 1). The preliminary results at MGH are quite encouraging.[5] By the end of June 1982, 38 patients with carcinoma at these sites had been treated. In 18 whose primary or recurrent rectal lesions were initially unresectable for cure because of tumor fixation, preoperative external-beam irradiation was followed by complete surgical resection (no microscopic residual disease) and intraoperative radiation therapy. In this group, there have not been any failures inside the intraoper-

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Table 2. Results of intraoperative radiation therapy for primary or recurrent carcinoma of rectum or rectosigmoid, Massachusetts General Hospital, as of September 1982

Type of resection	Number of patients	Number of failures Local	Any
Primary			
Complete resection	14	0	1
Prior incomplete resection	3	0	3
Microscopic residual disease	3	0	2
Gross residual disease	2	0	1
	22	0	7
Recurrent			
Complete resection	4	0	1
Prior incomplete resection	1	0	0
Microscopic residual disease	1	1*	1
Gross residual disease	6	2	4
No resection	4	4	4
	16	7	10

*Failure in external-beam field.

ative radiation therapy field, the area at greatest risk for local recurrence, or the external-beam field. In the same group of 18 patients, the three-year actuarial survival rate is about 94%. This figure is based on a small number of patients with a relatively short follow-up but is nevertheless encouraging.

Another subset of patients with primary or recurrent cancer had either incomplete resection before receiving any irradiation (and had no further resection) or had microscopic residual disease after resection. In this group as well, there have not been any failures in the intraoperative field. Unfortunately, in two of six patients who had gross residual disease and in all of four patients with unresected disease after surgery for recurrent cancer, there has been failure within the intraoperative therapy field. This suggests that maximal surgical resection may be an important component of local control.

Twenty-two patients with primary tumors have been treated, and there have not been any local failures in this group. The three-year actuarial survival rate in this subset is 68%. Not surprisingly, we have found that patients who have locally recurrent disease after low anterior resection or abdominoperineal resection do not do as well. Their overall

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survival rate is 38% at three years, and the incidence of local failure is higher (table 2).

The MGH series includes 20 patients with adenocarcinoma of the pancreas, 16 of whom have been treated with radiation therapy alone for unresectable tumor and the others with Whipple resection combined with irradiation. As might be expected, we have not done as well with local control in this group, as surgical resection of the bulk disease generally has not been done. Ten of the 20 patients have shown evidence of local failure. The overall median survival time is 13½ months, which compares favorably to the reported survival time following surgical resection.[11] Interestingly, the median survival time for patients receiving radiation therapy alone is 17½ months, longer than that for patients who also had surgical resection. Median survival time also is better than the nine months generally described with conventional radiation therapy combined with chemotherapy.[13]

Complications

Overall, the complications of intraoperative radiation therapy appear to be quite acceptable. We have not found any complications from the transport procedure. There have not been any difficulties with the anesthesia or any apparent increase in infectious complications secondary to transport.

There have been problems with delayed perineal healing in patients who have had infection in the pelvis or perineal wound after preoperative irradiation and abdominoperineal resection. The healing problems presumably are related to the advanced stage of tumor growth, the difficulty of the surgical resection, and the aggressive radiation therapy. Indeed, soft-tissue complications have been described in other series in which preoperative irradiation and resection were used for locally advanced tumors.[8-10] A few of our patients have required plastic surgical repair of the perineal wound because of a persistent draining sinus.

Early in our experience, gastric outlet obstruction developed in a patient with pancreatic carcinoma as a result of irradiation of most of the circumference of the duodenum. This complication has been avoided in subsequent patients by routine gastrojejunostomy in all instances of pancreatic carcinoma and by limitation of the amount of duodenum in the intraoperative irradiation field to the medial wall. Three patients have had evidence of gastrointestinal bleeding, one from a gastric ulcer secondary to inclusion of the distal portion of the stomach in the intraoperative irradiation field, one from the duodenum in an area within the intraoperative field, and the third from diffuse gastritis probably related to chemotherapy and external-beam irradiation. At present, bleeding problems are minimized by surgical movement of the stomach completely out of the boost field and by more cautious use of combination chemotherapy.

On the basis of laboratory experiments on a canine model, it appears that hollow viscera tolerate intraoperative irradiation poorly.[14] A serious risk of stricture in structures such as the ureter and bile duct with a single high dose of radiation was apparent, in contrast to the low incidence of ureteral stricture after conventional external-beam irradiation. Structures such as the stomach and the small and large intestine were observed to be at substantial risk for ulceration or strictures with doses greater than 2,000 rads. Functioning organ systems such as the liver and kidneys appeared quite susceptible to damage, with loss of function in the irradiated portions.

Overall, it appears that the tolerance of most of the retroperitoneal and pelvic soft tissues to intraoperative radiation therapy is quite good. Clinically, as we are usually dealing with residual disease in tumor beds (the primary tumor generally is removed), the organ systems mentioned usually can be effectively moved out of the path of the radiation beam without compromise of the desired extent of the radiation therapy field.

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Test Instructions

The following questions make up the CME examination based on the article "Progress in intraoperative radiation therapy" by Joel E. Tepper, MD, and Leonard L. Gunderson, MD. The intent of this test and its educational objectives are explained at the beginning of the article. There is one and only one correct answer to each test item. Please complete the test without referring back to the article. Answers must be submitted on authorized computer cards provided in the registration packet, and all cards must be postmarked no later than six weeks after receipt of issue. This article and examination have been reviewed and approved at Temple University School of Medicine, Philadelphia. **If you have not already registered for this CME program and wish to enroll, refer to the announcement on page 110.**

Test Items

1. Which of the following is a major advantage of intraoperative radiation therapy?
   a) Ability to use higher-voltage equipment.
   b) Ability to deliver a lower dose of radiation to the tumor.
   c) Increased ability to shield or remove normal tissues from the beam.
   d) Ability to give a higher radiation dose to both tumor and normal tissue.
   e) None of the above.

2. Which of the following tumors would be included in the study of intraoperative radiation therapy described?
   a) Unresectable rectal tumor.
   b) Unresectable rectosigmoid tumor.
   c) Locally advanced intra-abdominal tumor.
   d) Retroperitoneal soft-tissue sarcoma.
   e) All of the above.

3. Which of the following radiation doses (rads) is delivered intraoperatively?
   a) 500 to 1,000.
   b) 1,000 to 1,500.
   c) 1,000 to 2,000.
   d) 1,500 to 2,500.
   e) 2,000 to 3,000.

4. In which of the following groups of patients with locally advanced rectal and colonic carcinomas receiving intraoperative irradiation was the local failure rate the highest?
   a) Patients with gross residual disease after resection.
   b) Patients with microscopic residual disease after resection.
   c) *Patients with previous incomplete resection.*
   d) Patients with previous complete resection.
   e) There were no local failures in these groups.

5. Which of the following has *not* been a complication of intraoperative radiation therapy?
   a) Delayed perineal healing.
   b) Gastric outlet obstruction.
   c) Difficulties with anesthesia.
   d) Gastrointestinal bleeding.
   e) Persistent draining sinus.

6. Which of the following statements concerning conventional radiation therapy is correct?
   a) The likelihood of local tissue control is not related to the amount of radiation delivered to the tumor mass.
   b) New techniques such as interstitial radiation for head and neck tumors have not proved to be effective for tumor control.
   c) Techniques have been improved to increase dose delivered, but the incidence of complications related to irradiation of normal tissue has increased.
   d) In many situations the dose that can be administered is limited by adjacent normal tissue.
   e) All of the above are correct.

7. Which of the following statements concerning the success of intraoperative irradiation is correct?
   a) Previous resection had no effect on rate of local control.
   b) The more complete the resection, the better was the chance of local control.
   c) Rates of local control were the same *for patients with and without previous* resection.
   d) Success was greater in adenocarcinoma than in carcinoma of the rectum.
   e) Survival was not increased among the patients studied.

8. Based on laboratory experiments using a canine model, which of the following radiation dose levels (rads) should *not* be exceeded because of the risk of ulceration or stricture of hollow viscera?
   a) 1,500.
   b) 2,000.
   c) 2,500.
   d) 3,000.
   e) 3,500.

9. Which of the following statements concerning adenocarcinoma of the pancreas is correct?
   a) Conventional surgical treatment yields a 9% to 10% long-term survival rate.
   b) Eighty percent of patients coming to laparotomy have localized disease.
   c) Intraoperative irradiation is *not* indicated.
   d) Intraoperative irradiation combined with conventional radiation is indicated in cases of localized disease.
   e) None of the above.

10. Which of the following statements concerning intraoperative irradiation is *incorrect*?
   a) Clear plastic cylinders are used to retract normal tissues and confine the radiation beam.
   b) It is performed with the patient anesthetized.
   c) Electrons are used for irradiation.
   d) The need for intraoperative irradiation is determined at surgery.
   e) *A large single dose of radiation, generally about 4,500 rads, is delivered to the 90% isodose line.*

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