Discussion

DR. JOHN M. HOWARD (Toledo, Ohio): I rise to say that I think this is a very worthwhile evaluation, and it is, as has been stressed by the presenter, an evaluation. We are gaining a limited experience, performing the operation in the radiotherapy department.

Let me observe that this is not a minor operation. With a locally unresectable tumor, edema of the pylorus and the upper part of the duodenum may make gastric bypass difficult if one attempts to exclude the duodenum. If the gallbladder has been previously removed, the multiple bypasses plus the radiation exposure make for a major operation.

I would like to ask two questions: (1) Have you experienced, or are you particularly afraid of developing, duodenal necrosis, particularly as you increase your dose? Because if duodenal necrosis is a real threat, the operation becomes of greater magnitude.

And secondly, does the patient experience irradiation illness? You are giving a large dose to a limited area of tissue, excluding the liver, and it may be very interesting to note whether or not irradiation illness develops.

DR. WILLIAM P. LONGMIRE, JR. (Los Angeles, California): I want to thank the authors for the opportunity of reviewing their manuscript before this session. I am concerned, I think, more about the prospective use of this type of technique in the more hopeful type of case than the nonresectable cases that they have presented. The authors are attempting to evaluate the combination treatment of one of the most recalcitrant malignancies of the body, inoperable cancer of the pancreas, a tumor with an inherent biologic aggressiveness that so far seems to have thwarted our best efforts at surgical treatment, at least in a large majority of cases.

I think most of us have hoped, as each new diagnostic modality became available, that we would be able to diagnose this disease earlier and improve our results. Unfortunately, our experiences with CAT scans, endoscopic pancreatography, and ultrasound studies have failed to increase the incidence of early diagnosis, and even in those "earlier" cases seem to have failed to significantly alter the ultimate survival rate.

We are waiting, of course, to see whether NMR diagnosis will provide help, but I must say that I am a little bit pessimistic about that because, unfortunately, by the time the clinical symptoms of cancer of the pancreas suggest the use of these diagnostic techniques, this aggressive tumor is basically out of control.

Although some surgeons have achieved a limited improvement with more extensive excisional procedures, it would seem that for the near future our best chance of improving therapeutic results will be with some type of combination therapy, such as that which the authors are advocating in this series. And, hopefully, if applied to earlier cases, resection plus irradiation as they have utilized, and possibly with the addition of some chemotherapeutic agents, improved results might be achieved.

Although the number of cases is small, the follow-up period is brief, and the results would have been more clear-cut with some kind of a double-blind evaluation—for we have all seen cases of cancer of the pancreas that occasionally have remained asymptomatic for even a number of years after the diagnosis has been established—the results obtained with this treatment are interesting. We will await with considerable interest the long-term results with a larger number of patients.

DR. MURRAY F. BRENNAN (New York, New York): (Slide) During the period 1975 to 1980, 228 patients were explored by us for histologically proved exocrine pancreatic cancer. Thirty-three of those patients received an interstitial implant with I^{125}. There were seven major complications associated with that procedure, with one pancreatic fistula. All of the patients, however, had biopsy of the pancreas, concomitant bypass, and it was difficult to attribute the complication to the implant alone.

Median survival in that group was 8 months, with the longest survivor being alive at 33 months. This compares to the 18 months' survival for those patients resected, and 3 months to 4 months for those biopsied. The operative 30-day mortality in the implanted group was zero.

For the period 1969 to 1982, 72 patients have been treated with pancreatic implants at our institution. Sixty-eight of these had a primary pancreatic tumor, 65 adenocarcinomas, and three islet cell tumors. There was only one death in the postoperative period, from a cardiovascular accident.

(Slide) Life-table analysis suggested a 23% 2-year survival. Patients without known metastases at the time of operation and implantation have a 2-year survival of 26%.

We have begun a prospective study of this procedure and, in the 6 months of October 1983 to April 1984, we have explored 49 patients with adenocarcinoma of the pancreas. Eight of those have been resected, seven implanted, and 34 bypassed only. The majority of those bypassed had unsuspected metastases.

Are the authors suggesting from their data that intraoperative irradiation is ready for randomized study against resection, or bypass alone, given the median survival—certainly in excess of our own experience with resection—or are the results merely due to the inadequacy of staging that we all practice?

And finally, Dr. DeCosse has given me this slide (slide) to remind you all that a deceased member of this society, Dr. Leo Eloesser, was giving intraoperative irradiation therapy, I believe, in 1938 in San Francisco.

DR. A. RAHIM MOOSSA (San Diego, California): I will be a little bit more optimistic than usual. This is a preliminary communication reporting a small number of patients for a short time. Nevertheless, it is a landmark report to the Association.

The authors have shown appreciable palliation, both in terms of longevity and in terms of freedom from symptoms, for what is basically a dismal disease; and I believe the technique is also clearly applicable to other retroperitineal and gastrointestinal cancers.

It is worthwhile to comment that the authors report three major postoperative complications, and they were honest enough to attribute these complications to surgical technique and not to the radiation therapy. Although they have reported no disastrous complications from transporting the patient under general anesthesia from the operating room to the radiation therapy suite, I would like to know the mechanics of how they perform it so safely.

The implications for future trends and program development are enormous. If we can confirm their results, how should we plan for the future? Should we have a radiation therapy suite in the operating room, or should we build an operating room in the radiation therapy department?

The selection of patients is clearly important, since 47% of the patients explored by the authors were not given intraoperative radiation. Do they feel that maybe preoperative angiography will help them select the patients before surgery?

The next point that is emphasized in the paper is that a "double bypass" by gastrojejunostomy and by biliary/enteric anastomosis is essential. Do they recommend it before or after the intraoperative radiation therapy? Also when, if at any time, do they think a vagotomy should be added?

Finally, the most interesting part of this preliminary data, to me, is the use of the radiosensitizer. Could they elaborate on this concept to enable us, as surgeons, to understand what they are doing?

One last comment: Do the authors consider F.A.M. regimen chemotherapy as being responsible, at least partly, for their very good results?

DR. WILLIAM V. MCDERMOTT, JR. (Boston, Massachusetts): I think that this excellent report of Dr. Wood, Dr. Shipley, and their colleagues, has brought this particular modality of intraoperative radiotherapy to a point of credibility. I am impressed with the median survivals they are projecting and the results in local control.

Our experience, which is neither as long nor as extensive as theirs, dates back only 3 years, with 49 patients, of whom only 18 were primary unresectable carcinoma of the pancreas. I would hesitate on this group and with this duration to give any results beyond a few broad generalizations. Certainly, we have been impressed with palliation and relief of symptoms. We have had no postoperative—postradiation—compli-

cations that could be attributed to this modality. On the other hand, we have no documented evidence as yet for local control of the tumor, utilizing this intraoperative technique, supplemented by external beam radiation on an ambulatory basis over the subsequent days and weeks.

I would like to comment, however, on techniques. We have a room in the operating room suite dedicated to intraoperative radiotherapy, which I think has a great deal to offer in terms of practicality. The patient, when explored and found to be unresectable and suitable for intraoperative radiotherapy, has a planned, walled-off procedure, with a Bookwalter retractor maintaining organs in position and away from radiotherapy. Further protection can be utilized with flexible lead shielding. Then the orthovoltage radiation machine is docked on a lucite cylinder up to 10 cm, if the tumor can be encompassed by this particular size, which we find is about the maximum that is practical to use. The operating team and anesthesiologist can then retire behind protective, leaded glass walls, with the lines directed through the wall, and the patient monitored carefully under direct vision at a distance of a few feet.

We have had, as I say, no problems related to this, and are impressed with the potential for this technology. We began very cautiously with an intraoperative dose of 1200 rads, but with increasing confidence in the safety we have gradually increased this up to the level that you heard reported today.

I think it has a very real place in the treatment of pancreatic and other nonresectable cancers, and I think it is certainly going to come into increasing prominence in therapeutic oncology and the exact role and effectiveness defined much better. I am impressed with the fact that metronidazole may well have increased their results beyond what we have been able to achieve with other protocols.

DR. JOHN S. SPRATT (Louisville, Kentucky): My main points really constitute questions. As I heard the presentation, I gather these are rather large, localized neoplasms that are not otherwise resectable. The fact that a pancreatic cancer gets that big and is not disseminated suggests that it is biologically more favorable, and one of the things I would wonder is whether there is a breakdown by histopathological types. Particularly, are there a considerable number of rather indolent cystadenocarcinomas among this group?

And secondly, I would wonder whether the authors have tried to, in any way, correlate, say, the tritiated thymidine labeling index, or the mitotic index, of these neoplasms with survivorship.

The probability that the indolent, slower-growing cancers would be benefited by high dose flux is very low because there is a very small percentage of cells in the mitotic cycle of a slower-growing cancer at that time—which, you know, brings us full cycle. You will ultimately have to have a controlled clinical trial to show whether you are accomplishing anything with this technique.

DR. W. U. SHIPLEY (Closing discussion): It would be more appropriate if Dr. George L. Nardi, our senior surgical colleague, would answer all of these perceptive questions. However, he is too wise for that and has instead sent me up here. But I am very honored to have a chance to talk to the American Surgical Association. I will try and take these questions in order.

We did have complications, Dr. Howard. What we did not seem to have were the acute complications related to irradiation that were of major significance in the postoperative period. But we did have some late complications, 24% with upper GI bleeding, of a controllable nature except in one patient, who had a very compromised liver from metastases when he was bleeding (Table 5).

We have not seen any duodenal necroses. However, we have seen one duodenal obstruction whose site was in the intraoperative field. We have seen one duodenal bleeding of a slow nature, over many months, but controlled by a transfusion every month or so. Those are two direct, later effects on the duodenum. We find it not possible to exclude the medial wall of the first, second, or third portion of the duodenum, very often, from intraoperative radiation field because of immediately adjacent tumor.

We have seen postoperative delayed gastric emptying in two or three patients. It is unclear to us why that happens. We have gone ahead with the postoperative external beam radiation in the face of it, and those patients have regained adequate function.

I thank Dr. Longmire for his thoughtful, sage comments. We are using the F.A.M. chemotherapy. All but four of our patients received chemotherapy, either 5-FU or F.A.M., and there is a statistically significant difference in those patients that did get chemotherapy, compared to those that did not. We think this result may well be case selection rather than cytotoxic effect. But we do use chemotherapy when possible.

I thank Dr. Moussa for his very thorough evaluation. I think there were six questions; I will try and touch on them.

We have transported 120 patients up to now, and we have had seven superficial wound infections. We have not had any special surgical or anesthetic problems. A second major area of use of the intraoperative radiotherapy at the MGH has been in locally advanced, unresectable colon carcinoma.

Dr. Moussa asked for a short comment on the mechanism of action of the radiosensitizer misonidazole. The covalent bond-breaking damage of radiation is fixed in the presence of oxygen or another electron-affinic compound like misonidazole. If oxygen or such other compounds are absent, the chemical damage from the radiation is reduced by a factor of approximately three. Tumors, when they get large, do have areas in them that are short of oxygen. Normal tissue rarely does. Misonidazole is nonmetabolized, so that it can replace this missing oxygen in the hypoxic tumor cells, and theoretically will lead to a higher chance of cell death from radiation.

The reason misonidazole has been of no use in conventional fractionated radiation therapy is that there are only a minority of the tumor cells that are short on oxygen. Thus, unless you give a very big dose, as we do with intraoperative radiation, you are not selecting out those preferentially spared cells.

I am sorry not to have time to respond specifically to Dr. Brennan and Dr. McDermott. We agree with Dr. McDermott and Dr. Howard that the way to go is to have a dedicated unit in the operating room that is maximally available to the surgeons, and we are directing our attention towards obtaining this. We very much favor at this point the electron beam radiation from a linear accelerator rather than an orthovoltage beam. Orthovoltage is more convenient. However, we believe the dose distribution and the dose rate advantages of electron beam outweigh any of its inconveniences.