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External Beam plus Intraoperative Irradiation for Gastrointestinal Cancers

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Abstract. Although useful palliation can often be achieved when external beam irradiation and chemotherapy are used to treat locally advanced gastrointestinal malignancies, local control and long-term survival are infrequent in view of the limited tolerance of surrounding organs and tissues. In view of dose limitations of external beam irradiation, intraoperative irradiation (IORT) with electrons has been used as a supplement to external treatment in an attempt to improve the therapeutic ratio of local control versus complications. An IORT dose of 10 to 20 Gy has been combined with fractionated external beam doses of 45 to 55 Gy in 1.8 Gy fractions in studies performed in the United States, Japan, Europe, and Scandinavian countries. In this paper the indications for and the results of aggressive combined techniques that include IORT are discussed. Results obtained with external beam techniques alone or with chemotherapy and resection are presented by site to demonstrate the need for higher doses of irradiation. When results from IORT series are compared to standard treatment with regard to disease control and survival, local control appears better with locally advanced colorectal, gastric, and pancreatic cancer; and survival appears better with colorectal ± biliary cancers. With pancreatic cancer, improvements in local control do not translate into increased survival in view of the high incidence of subsequent liver and peritoneal failures. Implications for future strategies in all sites are discussed.

When gastrointestinal cancers are unresectable or residual disease exists after maximal resection, external beam doses necessary to accomplish local control are 60 to ≥70 Gy, which exceeds the radiation tolerance of some organs and structures in the abdomen and pelvis (stomach, small intestine, and spinal cord: 45 to 50 Gy for 5.0 to 5.5 weeks). Although portions of the large bowel and bladder can safely receive 60 to 70 Gy, the irradiated volume must be small or complications are excessive. If a portion of radiation is given at the time of a surgical procedure, all or part of the dose-limiting structures may be excluded by operative mobilization, shielding, or by use of variable electron-beam energies. The volume of the irradiation boost field is decreased by treating the tumor under direct vision and using appositional placement.

Whenever feasible, total or gross total resection of disease is performed before or after the external beam component of treatment. Resection is an almost uniform component of intraoperative irradiation (IORT)-containing regimens with both gastric and colorectal cancers but is rarely feasible with biliary and pancreatic cancers. Single-institution pilot studies are evaluating resection plus IORT following preoperative external irradiation and chemotherapy for initially unresectable pancreatic cancers.

The biologic effectiveness of single-dose IORT is considered equivalent to two to three times the same total dose of fractionated external beam treatment. The effective dose in the IORT boost field, when added to the 45 to 50 Gy delivered in 1.8 Gy fractions with external beam techniques, is 65 to 80 Gy for an IORT dose of 10 Gy, 75 to 95 Gy with a 15 Gy boost, and 85 to 110 Gy with a 20 Gy IORT dose.

Upper Gastrointestinal Cancers

Pancreatic Cancers

External Beam Irradiation ± Chemotherapy. For unresectable lesions, the use of external beam irradiation plus chemotherapy (CTx) results in a doubling of the median survival when compared with surgical bypass or stents alone (3–6 months median survival versus 9–13 months) and an increase in 2-year survival, from 0% to 5% to 10% to 20% [1]. However, 5-year survivors are rare, and local control is low. Even with external doses of 60 to 70 Gy, local failure was documented in at least two-thirds of the patients in a series from Thomas Jefferson University Hospital (TJUH) [2].

Intraoperative Irradiation ± External Beam Irradiation. The combination of external-beam irradiation (EBRT) plus intraoperative electrons or brachytherapy resulted in an improvement in local control in IORT electron series from the Massachusetts General Hospital (MGH) [3] and the Mayo Clinic [4, 5] and brachytherapy series from MGH [6] and TJUH [2], but did not translate into an improvement in either median or 5-year survival. In the Mayo Clinic IORT analysis [5], the local control rate at 1 year was 82% for EBRT plus IORT ± 5-fluorouracil (5-FU) versus 48% for EBRT ± 5-FU; at 2 years it was 66% versus 20%, respectively ($p = 0.0005$). This improvement did not translate into a difference in either median or 2-year survival (13.4 months median survival with IORT versus 12.6 months without; 12.0% versus 16.5%

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2-year survival). A higher percentage of patients in the non-IORT group did receive 5-FU during external irradiation. The lack of survival improvement was related to a high incidence of abdominal failure in both groups (20 of 37 IORT patients, or 54%, developed liver or peritoneal metastases versus 68 of 122, or 56%, in non-IORT patients). IORT analyses from MGH [6] and other institutions have also implicated distant failure as a significant problem (liver, peritoneum, or both).

Results in the brachytherapy plus external beam data from TJUH [2] paralleled the IORT data. Although local control was improved considerably with the addition of an iodine 125 implant to external beam treatment ± chemotherapy (78% versus 19%), median survival was the same (11.3 months versus 12.4 months).

In an attempt to improve patient selection and survival, investigators from the Mayo Clinic delivered the external beam plus chemotherapy component of treatment before restaging and exploration in a subsequent series [7]. In 27 patients who underwent IORT after the external beam treatment, local control was achieved in 21 patients (78%) with actuarial rates of 86%, 68%, and 45% at 1, 2, and 5 years, respectively. Median survival was 14.9 months with this sequence, and the 2- and 5-year survivals were 27% and 7%, respectively. These findings were compared with results in 56 patients who had IORT before receiving the high dose external component at the Mayo Clinic or elsewhere (median survival 10.5 months, 2-year survival 6%, $p = 0.001$). In an earlier Mayo Clinic analysis of 37 patients treated solely at that institution with the latter sequence, the median and 2-year survivals were, respectively, 13.6 months and 12%. Although the 2-year survival appeared to be improved with the altered sequence of preoperative treatment followed by IORT, it was presumably due to altered patient selection, as the relative incidence of liver plus peritoneal failures did not change (14 of 27 patients at risk, or 52%).

Future Possibilities. Pilot studies are currently being conducted at our institution in an attempt to decrease the incidence of liver and peritoneal failures by utilizing more aggressive chemotherapy. For patients with advanced disease, a four-drug combination is being tested in a North Central Cancer Treatment Group (NCCTG) Mayo Clinic pilot study—continuous-infusion 5-FU, daily oral leucovorin, mitomycin C, and dipyridamole (Persantine)—on the basis of single-institution response rates of about 40%. The two-drug combination of continuous-infusion 5-FU and oral leucovorin is being combined with external irradiation in a separate chemotherapy dose escalation pilot study (NCCTG/Mayo) for patients with locally unresectable lesions.

Gastric Cancer

External Beam Irradiation ± Chemotherapy. When external irradiation ± chemotherapy is utilized for gastric cancer patients with residual disease after resection or unresected lesions, most trials show an advantage for the combined modality treatment (irradiation plus chemotherapy) over single modality treatment (irradiation or chemotherapy alone). In a randomized series from Mayo Clinic, 5-FU was utilized during the first 3 days of external irradiation in half the group (irradiation dose of 35.0–37.5 Gy over 4–5 weeks plus a bolus of 5-FU 15 mg/kg for 3 days during week 1 of irradiation) [8]. In the combined modality patients the mean and overall survivals were improved: 13.0 months versus 5.9 months mean survival and 5-year survival in 3 of 25 patients (12%) versus 0 of 23 patients. In a subsequent randomized study by the Gastrointestinal Tumor Study Group (GTSG) [9, 10], a combination of irradiation and 5-FU followed by maintenance 5-FU/MeCCNU achieved better long-term survival than 5-FU/MeCCNU (3- and 4-year survivals of 18% versus 6–7%, $p < 0.05$). Although a second GTSG trial did not show a long-term survival advantage for combined modality treatment versus chemotherapy alone, 46% of patients did not undergo optimal irradiation, making results difficult to interpret. In a randomized European Organization for Research and Treatment of Cancer (EORTC) trial of external irradiation ± 5-FU, 22 patients had residual disease after resection [11]. The three long-term disease-free survivors (14%) received both radiation and 5-FU. A single-institution analysis (from MGH) also demonstrated a ≥10% long-term survival for patients with residual disease who were treated with irradiation plus chemotherapy [12]. In a University of Pennsylvania (UPenn) analysis of patients with unresected adenocarcinoma of the esophagogastric junction or esophagus [13], both local control and survival were better with combined modality treatment than with single modality treatment. Local control was achieved by irradiation alone in 1 of 23 patients (4%), by chemotherapy alone in 0 of 8 patients, and by combined modality treatment in 11 of 21 patients (52%). The median survival was 5 months with irradiation alone versus 10 months with combined modality treatment.

The initial GTSG analysis [9, 10] and one from MGH [12] suggested improved survival in patients with partially resected versus unresected lesions. In the GTSG series the 3-year survival was 25% versus 10%. In the MGH analysis, median survival after irradiation plus chemotherapy ± resection was 24 months with microscopic residual, 15 months with gross residual, and 14 months with no resection. Long-term survival at 3 years was 0% without resection versus 10% with resection but residual disease.

Intraoperative ± External Irradiation. For partially resected gastric cancer, the use of IORT alone or in conjunction with external beam treatment has yielded 5-year survival rates of 15% to 20%. Takahashi and Abe reported a Kyoto trial of surgery ± IORT in 211 patients in which subset analyses suggested survival advantages with IORT for Japanese stages II to IV [14]. The 5-year survival for stage IV disease in 27 patients treated with IORT was 15% versus 0% for 18 patients treated with surgery alone (three of the 4-year IORT survivors had proved residual disease). Five-year results with stages II and III were, respectively, 84% versus 62% and 62% versus 37%. In a single-institution pilot study from Pamplona [15], external irradiation ± chemotherapy has been combined with IORT in 48 patients (external doses of 46 Gy in 1.8 to 2.0 Gy fractions and the usual IORT dose of 15 Gy). Among 13 patients with stage IV disease, in-field relapse occurred in only 3. Two of eight patients with known residual after maximal resection were long-term disease-free survivors (22+ and 65+ months, respectively).

Randomized trials have also been reported from Beijing [16] and the National Cancer Institute in the United States (NCI) [17]. In the Beijing series, patients with stage III disease (serosal involvement or node-positive tumors) or stage IV disease (unresectable metastasis or adjacent organ involvement) were randomized to surgery alone or IORT (single dose of 25–40 Gy). In their

most recent report of 200 patients, a survival advantage with IORT was demonstrated only for stage III patients (65% versus 30% five-year survival; 52% versus 22% eight-year survival; $p < 0.01$). At the NCI, Sindelar and associates [17] performed a small randomized trial of IORT versus external irradiation following complete surgical resection (a surgery-alone control arm did not exist). This trial demonstrated improved local control with IORT but no survival benefit.

Future Possibilities. For patients with locally advanced gastric cancer (resection but residual or unresectable lesions), it seems reasonable to build on three positive segments of treatment data (external irradiation plus chemotherapy, IORT, neoadjuvant chemotherapy) and patterns of failure data. For patients with residual disease after resection, external irradiation plus chemotherapy or IORT ± external irradiation has controlled disease and produced long-term survival in 10% to 20% of patients in most single-institution analyses and randomized trials. These 5-year survival figures correlate well with the 20% of patients who relapse only in the locoregional area after complete surgical resection (i.e., no other components of relapse). Neoadjuvant chemotherapy for locally advanced disease has resulted in subsequent total resection of disease in ≥ 50% of patients in several European trials with EAP (etoposide/Adriamycin/cisplatin) or other regimens. However, the incidence of subsequent local regional relapse is ≥ 50% even after total resection. It would be of interest to merge these components of treatment. In patients with unresectable or borderline resectable disease on the basis of preoperative imaging studies, further evaluation of preresection "neoadjuvant" chemotherapy is reasonable. In patients with subsequent resection but residual tumor or resection but high risk factors (beyond the gastric wall, node-positive, or both), intraoperative or external irradiation or both could be evaluated in conjunction with further chemotherapy. A current Radiation Therapy Oncology Group (RTOG) pilot trial for such patients (RTOG 90-04) is utilizing two cycles of FAMTX (5-Fu/Adriamycin/methotrexate) neoadjuvant chemotherapy followed by maximal resection, IORT, and then external irradiation plus infusion 5-FU.

Biliary Cancer

External Irradiation ± Chemotherapy. Significant palliation and occasional long-term survival can be obtained with external beam irradiation of unresectable or recurrent lesions to doses of 4000 to 6000 cGy over 4.5 to 7.0 weeks, but permanent local control is uncommon [1, 18–21]. In view of the presence of dose-limiting organs (liver, stomach, duodenum, kidneys, spinal cord), the higher irradiation doses can be obtained with acceptable morbidity only if tumor extent is carefully defined with imaging studies and surgical clips and the patient is treated with sophisticated, multiple-field irradiation techniques. Areas of obstruction can be decompressed with placement of percutaneous transhepatic catheters, retrograde endoscopic stents, or intraoperative U tubes or by performing a surgical bypass such as a hepaticojejunostomy. However, none of these procedures actively treats the tumor. The addition of external beam irradiation to palliative drainage may prolong palliation and extend median survival, but long-term survival is infrequent.

Combinations of external irradiation and chemotherapy need to be evaluated more extensively in view of survival trends seen in an early analysis by Kopelson et al. [21] and a more recent series from the University of Pennsylvania and Fox Chase [22]. In the latter series, 1- and 3-year survival appeared to be better in patients with gross residual disease who received both modalities versus irradiation alone (1-year 65% versus 17%, 3-year 26% versus 8%, $p = 0.02$).

In patients with subtotal resection and residual disease, the addition of external irradiation may improve survival. The EORTC group [23] analyzed a group of 55 patients of whom 17 were treated with surgery alone and 38 received postoperative irradiation (52 of 55 had pathologically positive margins). The irradiated patients had a median survival of 19.0 months versus 8.3 months for those with surgery alone (1-year survival 85% versus 36%, 2 years 42% versus 18%, 3 years 31% versus 10%; $p = 0.0005$).

Specialized Irradiation Modalities. The usual tumor-related cause of death after external irradiation, with or without chemotherapy, is local persistence of disease. In view of the proximity of dose-limiting organs and structures, improvements in local control may be feasible with the addition of specialized boost techniques (brachytherapy via transhepatic catheters or retrograde endoscopic stents; intraoperative irradiation with electrons, orthovoltage, or high-dose brachytherapy) with or without irradiation dose modifiers. Pilot studies were instituted in our institution during the early 1980s using either transcatheter iridium or intraoperative electrons as boost techniques in combination with external irradiation ± 5-FU.

Transcatheter Brachytherapy ± External Irradiation. The temporary insertion of sealed radioactive sources via transhepatic catheters or stents placed endoscopically can deliver localized high-dose irradiation and is attractive because of its potentially wide applicability (in contrast to that of intraoperative electrons). There is a suggestion of improved survival in patients treated with both external beam irradiation and brachytherapy when compared with either modality alone [1, 24, 25], but no randomized trials have been performed to test these possible differences. Deaths due to sepsis are reported more commonly than in external-beam-only series, which is a reflection of the need for transhepatic catheters in all patients with inherent risks. In view of the short follow-up and the low incidence of survival beyond 1 year, the exact incidence of locoregional failure is difficult to determine. In a Mayo Clinic series [18] in which 10 patients received external irradiation up to 45.0 to 50.4 Gy followed in 2 to 4 weeks by a transcatheter boost of 20 to 25 Gy (calculated at a 1.0 cm radius in 9 of 10 patients and a 0.7 cm radius in the other) local failure was documented in three patients (≥ 30% risk).

IORT ± External Irradiation. In the U.S. series using intraoperative electrons or orthovoltage for primary bile duct lesions, most patients have received both external beam and intraoperative irradiation. In the Rush Presbyterian series, two of five patients survived ≥ 18 months [26]. The single disease-free survivor (40+ months) was the only patient in their series to receive chemotherapy during the external irradiation. In a Mayo Clinic series of 15 patients with unresectable tumors at risk ≥ 1 year [27, 28], median survival was encouraging at 16.5 months for the entire group and

at 18.5 months in the 14 patients treated with curative intent (one patient was a 5-year survivor). Five of the fourteen patients treated with curative intent (36%) were alive at 2 years. Local tumor persistence or relapse was diagnosed in 6 of the 14 treated with curative intent (43%), but in 3 who died of noncancer causes it was documented only at autopsy (15.0, 21.5, and 37.0 months, respectively). Only three patients received 5-FU during external irradiation. In a Harvard Joint Center analysis [29], median survival was 14.0 months, and local progression or persistence was documented in 50% of evaluable patients.

The potential impact of treatment method on duration of survival is seen in separate series from Japan and the Mayo Clinic. In the series from Japan by Iwasaki and colleagues [30], with biliary drainage alone (21 patients) the survival at 6 months was only 20%, with a 1-year survival rate of ≤ 5% and no 18-month survivors. With noncurative resection ± IORT (13 patients each group) or biliary drainage plus IORT (6 patients), survival appeared to be better (1-year survival 44%, 46%, and 33%; 2-year survival 8%, 15%, and 17%). Data from the Mayo Clinic [18, 27, 28] showed that survival at ≥ 18 months was 0% with external irradiation ± 5-FU (11 patients), 33% with gross total or subtotal resection before external irradiation (6 patients), and 30% and 45%, respectively, in patients with unresectable lesions treated with external irradiation plus a specialized boost with iridium 192 (10 patients) or IORT electrons (14 patients). There were two 5-year survivors in the latter group of 24 patients.

Future Possibilities. In an attempt to improve survival and disease control, it would be of interest to combine the various modalities that appear to affect those endpoints. For unresectable lesions these options include external irradiation, simultaneous ± maintenance chemotherapy, and a specialized irradiation boost with transcatheter iridium or intraoperative electrons. The increased utilization of simultaneous external irradiation plus chemotherapy is indicated in view of results in single-institution studies in patients with bile duct cancers and randomized single-institution and group trials at other gastrointestinal sites (unresectable pancreas cancer; unresected or residual gastric and large bowel cancer; resected but high-risk rectal and pancreas ± gastric cancer; unresected esophageal cancer). With regard to the use of IORT versus brachytherapy for a specialized boost, if the boost can safely be given via the transcatheter approach it would be a more cost-effective method of delivery. If stomach or duodenum cannot be excluded from a brachytherapy field, it may be reasonable to reoperate for the purpose of giving the boost with IORT electrons while displacing those structures.

For patients in whom residual disease remains after an attempt at resection, the addition of external irradiation ± chemotherapy seems reasonable on the basis of analyses by Gonzalez et al. (for the EORTC group) [23] and Weiss et al. (Fox Chase/UPenn) [22]. The availability of intraoperative electrons or high dose rate (HDR) brachytherapy may allow delivery of a localized boost dose of irradiation after resection but before reconstruction (i.e., IORT electrons for positive radial or circumferential margins due to adherence to porta hepatis structures that could not be boosted with postoperative transcatheter iridium; HDR brachytherapy for microscopically positive ductal margins).

Colorectal Cancer

External Irradiation ± Chemotherapy Resection

External-beam irradiation has been combined with surgical resection and systemic treatment for locally advanced colorectal cancers. In separate series from Princess Margaret Hospital (PMH) [31] and the Mayo Clinic [32], using radiation alone (PMH, Mayo) or combined with systemic therapy (Mayo), the local recurrence rate was 90% or higher in evaluable patients. Although a combination of irradiation (± 5-FU) with surgery for residual disease after subtotal resection or for initially unresectable disease produces a local control rate better than that with no resection, the risk of local recurrence remains high, at 30% to 50% [33–36].

IORT ± External Irradiation

In an attempt to decrease local recurrence and improve survival, institutions in the United States [34–40], Europe [41], Japan, and Scandinavia have combined an intraoperative electron boost with fractionated external-beam doses of 45 to 50 Gy in 1.8 Gy fractions, with or without resection. In U.S. studies, the IORT dose varies from 10 to 20 Gy depending on the amount of disease remaining after an attempt at resection: with microscopic residual, 10.0 to 12.5 Gy; with gross residual of < 2 cm, 15.0 Gy; and with gross residual of ≥ 2 cm or unresectable, 17.5 to 20.0 Gy.

In an initial MGH report of 32 patients treated with external irradiation, maximal resection, and IORT [34], 16 patients with initially unresectable primary lesions underwent external irradiation before resection and IORT. When results were compared with historical controls treated only with external irradiation and resection, survival at 1 and 2 years was statistically better in the IORT patients, and disease relapse within irradiation fields was 0% and 43%, respectively, (IORT versus non-IORT). Patient selection appeared similar, as about 75% of patients in both groups had gross pathologic tumor extension beyond the muscularis propria following preoperative irradiation.

In updated MGH IORT analyses [37, 38], 5-year actuarial survival among 42 patients with locally advanced primary rectal cancers was 43%, whereas among 30 patients with locally recurrent lesions it was 19%. The latter data exceed the expected long-term survival of ≤ 5% when locally recurrent tumors are treated with standard techniques. In patients with primary lesions, both 5-year actuarial local control and disease-free survival seemed better if the surgeon was able to accomplish a gross total resection prior to IORT (Table 1). With recurrent disease, patients with any degree of residual disease had 5-year local control and disease-free survivals of only 11% and 6%, respectively, whereas the respective figures for patients with clear resection margins were 42% and 33%. Published data from Rush Presbyterian [39], the RTOG [40], and Pamplona [41] also support the correlation between local tumor control and the amount of residual disease after maximal resection.

Mayo Clinic Results: External Irradiation Plus IORT

Results have been compared in sequential series of Mayo Clinic patients with locally advanced primary colorectal cancers treated by surgical resection and external beam irradiation alone (17 patients) [33] or in conjunction with IORT (20 patients) [35, 36].

Table 1. Colorectal IORT: tumor failure in IORT or external irradiation field versus amount of residual.

Series	No. of pts.	CF or LF (%)		Residual vs. CF or LF (%)		
		Primary	Recurrent	None	Res (m)	Unresect or Res (g)
MGH [37, 38], 5-year actuarial						
Primary	42	23	—	12	31	50
Recurrent	30	—	74	58		89
Rush Presbyterian [39]						
Primary	9	33	—	—	14	100
Recurrent	35	—	54	—	39	64
RTOG [40] (recurrent)	37	—	62	—	33	89
Pamplona (recurrent)	27	—	74	—	50	84

Modified from Gunderson and Dozois [36].

IORT: intraoperative irradiation; CF: central failure in IORT field; LF: local failure in external beam field; Res (m): microscopic residual; Res (g): gross residual; Unresect: unresectable.

All relapses in non-IORT patients occurred before 18 months, and IORT patients were at risk for at least 2 years. Apparent improvements in local control with the addition of IORT (80% versus 24%) seemed to translate into improved survival, with a doubling in both median survival (37 months versus 18 months) and 3-year survival (50% versus 24%). Although the differences seen may reflect selection bias in nonrandomized series instead of treatment effect, it may be difficult to test these parameters in randomized trials.

Data supporting the use of IORT for locally recurrent disease is found in a Mayo Clinic analysis of 106 patients with palliative resection of locally recurrent rectal cancers from 1981 to 1988 [36, 42]. None of the patients had evidence of extrapelvic disease, and 43 received IORT as a component of treatment. The IORT dose was 15 to 20 Gy in 39 of 42 patients. In 34 of 42 IORT patients (81%) there was gross residual disease after attempts at resection, and microscopic residual existed in the remaining 9. External irradiation was applied to 41 patients (doses of $\geq$ 45 Gy in 38 patients). Significant factors with regard to 3- and 5-year survivals included the amount of residual (microscopic versus gross, 33% versus 9%, $p = 0.032$); IORT versus none (19% versus 7%, $p = 0.0006$); type of symptoms (asymptomatic versus symptomatic without pain versus symptomatic with pain, 49% versus 0% versus 8%, $p = 0.0075$); type of fixation (none versus one, two, or three or more sites, 67%, 20%, 6%, and 0%, $p = 0.0001$); and preoperative ECOG status ($p = 0.03$). The 5-year cumulative probability of distant metastasis was 65.6% with a crude incidence of 42.0%.

Future Possibilities

Although encouraging trends exist with regard to improvement in local control and possibly survival when IORT results are compared with standard treatment approaches for locally advanced primary and recurrent colorectal cancers, the incidence of systemic failure is approximately 50%, and local failures within the IORT and external irradiation fields are significant if a gross total resection is not surgically feasible. In an attempt to improve local control, it seems reasonable to consistently deliver 5-FU ± leucovorin or other enhancing or additive agents during external irradiation and to evaluate the use of dose modifiers in conjunction with IORT (e.g., sensitizers, hyperthermia). In view of the high systemic failure rates, more aggressive chemotherapy should be evaluated during external irradiation as well as after its completion. Although it would be of scientific interest to randomly compare standard treatment ± an IORT electron boost, such trials have not accrued well in the United States but are being attempted in Europe and Scandinavian countries. Many patients are referred to U.S. IORT institutions in order to receive IORT electrons, not for the potential of randomization to IORT-containing treatment arms. Trials that are feasible in the United States are those in which the aggressive local treatment consists of external irradiation, resection, and intraoperative irradiation; and the randomization tests optimal chemotherapy during and after external irradiation, as well as testing the presence or absence of dose modifiers during IORT. A randomized trial is in progress by the RTOG that will test the efficacy of the hypoxic cell sensitizer etanidozole (SR-2508) in conjunction with IORT for locally recurrent colorectal cancers (all other treatment factors will be constant).

Résumé

Bien que l'irradiation externe et la chimiothérapie peuvent procurer une bonne palliation dans certains cancers digestifs étendus, le contrôle local et la survie à long terme ne sont pas souvent améliorés en raison de la tolérance limitée des organes et des tissus de voisinage. En raison de ces limitations, l'irradiation intra-opératoire a été utilisée pour pallier les inconvénients de l'irradiation locale et augmenter les effets locaux. Dans les essais faits au Japon, en Europe, dans les pays Scandinaves comme aux Etats Unis, l'irradiation intra-opératoire comporte une dose de 10 à 20 Gy combinée avec des doses d'irradiation externe de 45 à 55 Gy par fractions de 1.8 Gy. Dans ce travail, les indications d'un traitement agressif comprenant une irradiation intra-opératoire sont discutées. Les résultats obtenus par irradiation externe seule ou avec la résection associée à la chimiothérapie sont présentés selon le site du cancer primitif pour démontrer le besoin d'accroître le doses d'irradiation. Lorsque les résultats de l'irradiation intra-opératoire sont comparés aux résultats du traitement standard, le contrôle local apparaît meilleur en cas de cancers colorectal, gastrique et pancréatique alors que la survie semble meilleure lorsque le cancer est colorectal ou biliaire. En cas de cancer pancréatique, l'amélioration du contrôle local ne retentit pas sur la survie car le taux d'ensemencement hépatique ou péritonéal est élevé. Les implications pour l'avenir sont discutées site par site.

Resumen

Aunque es común lograr una paliación útil en pacientes sometidos a irradiación y quimioterapia como tratamiento de los neoplasmas gastrointestinales localmente avanzados, son infrecuentes tanto el control local como la sobrevida a largo plazo, en razón de la limitada tolerancia de los órganos y tejidos vecinos. En vista de las limitaciones de dosificación de la irradiación externa, se ha utilizado irradiación intraoperatoria (IIOP) con electrones como terapia suplementaria de la irradiación externa en un

intento por mejorar la relación entre el control local y las complicaciones. En diversos estudios realizados en Estados Unidos, Japón, Europa y los países escandinavos se han utilizado dosis IIOP de 10 a 20 Gy en combinación con dosis fraccionadas de irradiación externa de 45 a 55 Gy, en fracciones de 1.8 Gy. En el presente artículo se discuten las indicaciones y resultados de agresivas técnicas combinadas, incluyendo IIOP. Se presentan los resultados obtenidos con las técnicas de irradiación externa o con quimioterapia e irradiación de acuerdo con la ubicación del neoplasma, para demostrar la necesidad de dosis más altas de irradiación. Cuando se comparan los resultados de la serie de IIOP con el tratamiento estándar en relación al control de la enfermedad y a la supervivencia, el control local aparece mejor en el cáncer colorrectal localmente avanzado, el cáncer gástrico y el cáncer pancreático y la sobrevida aparece mejor en los cánceres colorrectal ± cánceres biliares. Con el cáncer pancreático, los superiores resultados en cuanto al control local no se traducen en prolongación de la sobrevida por razón de la alta incidencia de fallas hepáticas y peritoneales subsiguientes. Se discuten las implicaciones para futuras estrategias en las diversas ubicaciones del cáncer gastrointestinal.

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