ADJUVANT RADIATION THERAPY FOR PANCREATIC CANCER

Despite advancements in diagnostic tools, understanding of cellular mechanisms and invention of novel systemic therapies, carcinoma of the pancreas remains one of the greatest challenges for clinicians. It is the fourth leading cause of cancer death in the United States with less than 5% of patients surviving at five years after diagnosis and a case fatality index of more than 90%. Surgery offers the only means of cure but only 15-25% of patients present with tumors amenable to resection. Historically, patients undergoing resection of localized pancreatic carcinoma have a long term survival of approximately 20% and a median survival of 13 to 20 months, with the best results being restricted to centers with high volumes of this cancer. These appalling survival figures for this cancer can be attributed to advanced stage at presentation in more than 80% of patients and its aggressive biological phenotype that is resistant to all forms of therapy. Recent data suggests that the survival of patients who undergo resection may be improving, with contemporary 3 year survival rates around 30%, possibly due to advances in surgical and perioperative care, though some investigators believe that these estimates are overly optimistic.

Surgical resection as part of a multimodality treatment approach for patients with resectable pancreatic cancer represents the only potentially curative treatment strategy. For patients undergoing potentially curative surgery, three major sites of disease relapse dominate: the bed of pancreas (local recurrence), the peritoneal cavity and the liver. High local failure rates of 50-86% occur despite resection because of frequent retroperitoneal soft tissue infiltration resulting in the inability to achieve wide retroperitoneal soft tissue margins secondary to anatomic constraints to wide posterior excision posed by superior mesenteric vessels, portal vein and inferior vena cava. High incidence of lymph node involvement is another factor contributing to this dismal scenario. Careful pathological examination of the posterior peripancreatic soft tissue margins indicates a high incidence of microscopic residual disease extending to these margins in patients undergoing resection. Thus, adjuvant radiation therapy along with chemotherapy would appear to be a logical choice for these patients and hence has been pursued actively but dose limiting organs like small intestine, stomach, liver, kidneys and spinal cord have prevented delivery of tumoricidal doses in past due to increased risk of serious acute and long-term complications. Combined chemotherapy and radiation further increased this risk.

Radio biologically suboptimal split course radiation therapy in inadequate doses was employed most of the times to overcome the limitations of delivery systems. Consequently, adjuvant radiation therapy, despite its sound clinical rationale, was not proven to be beneficial. Some studies in fact found radiation to be detrimental. Modern radiotherapy using multifield conformal radiotherapy helps to reduce dose to most of these organs leading to reduction in treatment related morbidity, thus permitting delivery of higher external beam radiation doses than were previously possible. The role of adjuvant radiation needs to be revisited in light of this fact and previous literature needs to be interpreted accordingly.
A review of literature reveals that despite several prospective trials and single institution experiences, it is difficult to establish a definitive role for adjuvant radiation therapy as all of these trials either are limited in size or have other major methodology problems and hence have limited or no contemporary value. It is pertinent to go into the details of these trials while defining adjuvant role of radiation therapy for resectable pancreatic cancer.

**PROSPECTIVE TRIALS**

**THE GASTROINTESTINAL STUDY GROUP (GITSG) TRIAL**: This was the first prospective trial of adjuvant chemo radiotherapy (CRT) for patients with completely resected pancreatic cancer (ampullary cancer excluded) and negative surgical margins. Started in 1974, it randomized patients to chemoradiation or observation only. External beam radiation therapy (EBRT) dose of 40 Gy was delivered in split-course (two weeks gap halfway through) fashion with concurrent 5-flourouracil (5-FU) 500mg/m² given as an intravenous bolus on the first three days of each course of radiation therapy, followed 1 month later by maintenance 5FU given weekly for two years or until disease progression. Patients were stratified at the time of randomization by the type of surgical procedure, degree of differentiation, stage of disease, and location of primary tumor. Ninety five percent of patients had cancer of the head of pancreas, and 28% had node positive disease. This trial was stopped early secondary to slow accrual (43 patients over 8 years) and a positive interim analysis at a median follow-up of 5.5 years showing that patients treated on the CRT arm experienced a survival benefit (median survival of 21 months versus 10.9 months (p=.035), 2 year survival of 43% versus 18% and 5 year survival of 15% versus 5%). There was also a significant difference in survival favoring those patients who had disease confined to the pancreas compared with those with regional involvement and for those patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 compared with those with a performance status of 3 to 4. In an effort to address the low patient numbers, an additional 30 patients with same characteristics but better performance status were later enrolled to receive adjuvant CRT. These additional patients confirmed the survival benefits of original trial.

**COMMENTS**: The GITSG trial has been criticized for many reasons.

1. It was terminated early without meeting its accrual goals due to slow accrual and high drop out rate and thus the number of patients was small.
2. Only 9% of the patients received the planned 2-year maintenance chemotherapy and the radiation dose was low/split course (sub-optimal by modern standards).
3. It had an unusually poor survival rate for control group.
4. Twenty five percent of patients did not begin adjuvant therapy until over 10 weeks after resection and 32% of the original treatment arm had violations of the scheduled radiation therapy.
5. There was patient selection bias on performance status.
6. The second study was inferior as it was not properly randomized.
7. This trial was not designed to examine the benefits of the individual components of adjuvant therapy (chemotherapy versus chemoradiotherapy); so it is unclear from where most benefit, if any, was derived.
An interesting observation was the fact that the local recurrence rate was between 30-50% and the rate of hepatic metastasis was between 40-50% in all patients treated, whether they received adjuvant treatment after surgery or not. This suggests that though adjuvant treatment produced beneficial effect, but the dose of radiation was inadequate to deal with the burden of infield disease, and the 5-FU alone was unable to eradicate systemic in most of the patients. Nevertheless, this trial resulted in CRT being accepted as appropriate adjuvant therapy for resected pancreatic cancer in the United States.

EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC) TRIAL 40891: This trial was conducted between 1987 to 1995 by Gastrointestinal Tract Cancer Cooperative Group of EORTC to confirm the findings of the original GITSG study. In this study, 218 patients with resected pancreatic or other periampullary cancers were randomly assigned to receive 40 Gy of EBRT in same split dose fashion as the GITSG trial with concurrent continuous infusional 5-FU 425mg/ kg for 5 days at beginning of each radiation course or observation alone. No adjuvant chemotherapy was given. This study included patients with positive surgical margins and 50% had positive lymph nodes. It showed no significant improvement (p=.208) in median survival (24.5 versus 19 months), 2 year survival (51% versus 41%) or 5 year survival (28% versus 22%). Only 114 of the enrolled patients had pancreatic cancer, with the remaining patients having periampullary tumors. Subset analysis of the patients with primary pancreatic cancers showed a median survival of 17.1 months for treated patients versus 12.6 months for control group (p=.099) and 2 year survival of 34% for treated patients versus 26% for the control group (p=.099). The authors concluded that “routine use of adjuvant chemoradiotherapy is not warranted as standard treatment in cancer of the head of the pancreas or periampullary region.”

A subsequent 12 year follow up of results of the EORTC trial was published in 2007. The results showed that the median OS was 1.8 years versus 1.6 yrs (p not significant) and the 5 yr survival was 25% versus 22% (p not significant). The authors concluded that there was no benefit with adjuvant treatment.

COMMENTS: This trial was interpreted as a negative study but it had several limitations.

1. Inclusion of patients with periampullary cancer resulted in dilution of results of this trial since the behavior of this cancer varies from that of pancreatic cancer and generally has a better prognosis.
2. Patients with positive surgical margins were allowed with no prospective assessment.
3. The number of patients was small and thus the trial was significantly underpowered to detect a difference in treatment outcome for the subset of patients with pancreatic cancer.
4. The radiation dose was low and its delivery was in a suboptimal split course fashion.
5. Twenty percent of patients assigned to the treatment arm never received treatment. In addition, 35 patients in the treatment arm received only 3 days of 5-FU during the second course of radiation. No maintenance chemotherapy was given in the treatment arm.

Although this trial showed no benefit with adjuvant CRT but it left many questions unanswered.

**THE EUROPEAN STUDY GROUP FOR PANCREATIC CANCER-1 (ESPAC-1) TRIAL**: This is the largest and most recent randomized trial that was conducted to answer several questions about adjuvant therapy for pancreatic cancer. The trial design was complex where treating physicians were allowed to enroll their patients into one of three parallel randomized arms

1. Chemoradiation versus observation (n=69), consisting of 20Gy over 2 weeks with 5-FU 500 mg/m² on days 1 through 3, then repeated after a two week break;
2. Chemotherapy versus observation (n=92), consisting of bolus 5-FU 425 mg/m² with leucovorin 20 mg/m² given for 5 days every 28 days for 6 months;
3. A 2 by 2 factorial design of 289 patients enrolled on chemoradiotherapy (n=73), chemotherapy (n=75), chemoradiotherapy with maintenance chemotherapy (n=72) or observation.

A total of 541 patients were randomized and were stratified by margin status at initial randomization. The primary end point was to look for an improvement of 20% to 40% in the 2 year survival rate in patients with negative margins. The initial report of this study described the interim results for 541 patients at a median follow-up of 10 months. The primary endpoint of 2-year survival for margin negative patients was not reported in the main analysis of this trial. The data from the treatment groups from all three parallel trials were pooled for analysis. There was no survival difference between the 175 patients who received adjuvant chemoradiation and the 178 patients who did not receive it (2-year survival rate for patients receiving chemoradiation was 29%, compared with 40% for those not receiving it, 5-year survival was 10% versus 20% p=.05 and a median survival 15.5 months versus 17.9 months; p= .24). There was however a survival benefit found for patients who received adjuvant chemotherapy (n=238) compared to those who did not (n=235) (median survival 19.7 months versus 14 months; p=.0005). On further follow-up, the 5-year survival rate for patients who received chemotherapy was 21% versus 8% for those who did not.

**COMMENTS**: ESPAC1 trial can be criticized on many counts;

1. Physicians were allowed to choose which of the three parallel trials to enroll patients on, thus creating potential bias
2. Patients could receive “background” chemoradiation or chemotherapy as decided by their physician. Approximately one third of the patients enrolled on chemotherapy versus no chemotherapy trial received “background” chemoradiotherapy or chemotherapy
3. To increase patient numbers, 68 patients were assigned separately and randomized to either chemoradiotherapy or observation, and 188 patients were separately assigned to either chemotherapy alone or observation.
4. Radiation was given in a split course fashion, with the treating physician judging
the final treatment dose (40 Gy versus 60 Gy). Also, there was no central review of radiation ports for quality assurance purposes. So this trial may not tell us much about the role of modern radiotherapy regimens in the adjuvant setting.

5. In the chemoradiation versus no chemoradiation arm, no maintenance adjuvant chemotherapy was given, similar to the EORTC trial.

6. The study did not have enough statistical power to perform comparisons between each of the 4 arms that result from the 2x2 randomization schema.

An updated analysis that included only the 289 patients who underwent strict randomization was reported at a median follow-up of 47 months in 2004\textsuperscript{29} which concluded that there was a benefit with adjuvant chemotherapy (median survival 20.1 months versus 15.5 months for observation – \( p=0.009 \)) but chemoradiation had a deleterious effect on survival (15.9 months versus 17.9 months with observation – \( p=0.05 \)). The authors reported that the study was not powered to allow statistical comparisons between the 4 treatment groups.

It is interesting to know that the surgery alone arm in ESPAC1 did exceedingly well (median survival 16.9 months versus 11-13 months for other randomized trials) and chemoradiation arm did exceptionally poorly (median survival 13.9 months versus 17.1 months for EORTC trial). The reasons for this are not clear and hence this data needs to be viewed with caution.

Additional data from this trial and some composite data from the ESPAC-1 trial and ESPAC-3(v1) trial were reported in 2009\textsuperscript{30} and these results recapitulate the results reported earlier.

ESPAC data has been extensively reviewed and criticized for the substandard radiation given and for the inappropriate toxicity reporting. There was also a longer time of treatment in the chemoradiation arm and the inclusion of patients with margins positive which could all lead to poorer survival.\textsuperscript{31}

To resolve the issue, a meta-analysis of 5 randomized trials for adjuvant therapy was published in 2005 by the Pancreatic Cancer Meta-analysis Group.\textsuperscript{32} The individual patient data from these trials as well as previously unpublished data from ESPAC-1 on 261 patients was studied. The results mirrored those of ESPAC-1. The pooled estimate of the hazard ratio (HR) indicated a 25% significant reduction in the risk of death with chemotherapy (HR=0.75, \( p=0.001 \)) with median survival estimated at 19 months with chemotherapy and 13.5 without. The pooled estimate of the HR indicated no significant difference in the risk of death with chemoradiation (HR=1.09, \( p=0.43 \)) with median survivals estimated at 15.8 months with chemoradiation and 15.2 without. The 2- and 5-year survival rates were estimated at 30 and 12%, respectively, with chemoradiation and 34 and 17% without. Subgroup analyses estimated that chemoradiation was more effective and chemotherapy less effective in patients with positive resection margins. These results show that chemotherapy is effective adjuvant treatment in pancreatic cancer but not chemoradiation.

COMMENTS: There were several shortcomings of this meta-analysis. There was heterogeneity between trials ascribed to differing patient populations with specific tumor characteristics, specifically the recruitment of resection margin-positive patients. The
radiotherapy was substandard in all the trials. The results were also influenced by disproportionately high patient numbers in the ESPAC-1 trial.

A study published in 2008[^33] utilized the Surveillance, Epidemiology, and End Results registry to identify 1930 patients with No pancreatic adenocarcinoma who had undergone curative surgical resection from 1988 to 2003. Results showed that patients who received radiotherapy had better survival as compared to those who did not get it (20 months versus 15 months, p<.001) and radiation emerged as an independent predictor of improved survival in the multivariate analysis. Although this study supports the use of adjuvant radiation, being non-randomized in nature makes its conclusions circumspect in the modern era of evidence based medicine. Historically, all these trials have used 5-FU concurrently along with radiation. The approval of Gemcitabine as a single agent for pancreatic cancer was an important advance that prompted its use in the adjuvant setting with radiation in most modern contemporary trials.

**RADIATION THERAPY ONCOLOGY GROUP (RTOG) TRIAL 9704[^37]:** This phase III intergroup study, enrolled 538 patients with resected pancreatic cancer, with 75% of patients having T3 or T4 disease, 66% having node positive disease and one third with positive margins. Randomization was performed after surgery and was stratified by tumor diameter (<3cm or ≥ 3 cm), nodal status and surgical margins. Patients were randomized to either: (a) 3 weeks of continuous infusional 5-FU at 250 mg/m²/day followed by chemoradiation (50.4 Gy in 1.8 Gy daily fractions with continuous infusional 5-FU at 250 mg/m²/day), then two four week courses of continuous infusional 5-FU at 250 mg/m²/day beginning 3-5 weeks after completion of chemoradiation with two weeks rest between courses, or (b) three weekly doses of gemcitabine at 1000 mg/m² followed by same 5-FU based chemoradiation as in the first arm, followed by three months of Gemcitabine 1000 mg/m² given weekly 3 out of every 4 weeks. Results showed a survival advantage in patients with resected pancreatic head carcinoma receiving maintenance gemcitabine versus maintenance 5-FU (median survival of 20 months versus 17 months and 3 year survival of 36% versus 21%) but there was 14% grade 4 hematological toxicity.[^38]

**COMMENTS:** Although this trial addressed many of the methodologic limitations of earlier trials (large numbers, adequate power, prospective quality assurance procedures including central review of preoperative computed tomography scans and radiation therapy fields before the initiation of chemoradiation, adequate radiation dose), it unfortunately did not address the issue of whether chemoradiotherapy added any benefit or was detrimental to patients as suggested by ESPAC-1 trial.

**EORTC TRIAL 40013[^39]:** This randomized phase II trial comparing gemcitabine alone with gemcitabine plus radiation using modern chemoradiation techniques was presented at ASCO 2009. Ninety patients were randomized to chemotherapy or to chemoradiation. Both arms had same overall survival of 24 months but there was a significant improvement in local control with the use of chemoradiation. However, local control is of limited benefit when systemic disease is the main determinant of survival. Hence it may
be difficult to demonstrate benefit for radiation until systemic treatment of pancreas cancer improves.

**SINGLE INSTITUTION EXPERIENCES**

Several reports of single-institution experiences with adjuvant therapy for pancreatic cancer have provided additional evidence to the benefit of adjuvant therapy.

**Johns Hopkins Medical Institution Experience**\(^{40}\): This is the largest series of this type where investigators reported the results of a retrospective analysis of 174 patients treated as follows:

1. EBRT (40-45 Gy) with two 3-day courses of 5-FU at the beginning and the end of radiation, followed by weekly bolus 5-FU (500 mg/m\(^2\)) for 4 months (n=99)
2. EBRT (50.4 Gy to 57.6 Gy) to the pancreatic bed plus prophylactic hepatic irradiation 23.4 Gy to 27 Gy given with infusional 5-FU (200 mg/m\(^2\)/day) plus leucovorin (5mg/m\(^2\)/day) for 5 out of 7 days of the week for 4 months (n=21), or
3. No therapy (n=53)

Patients who received adjuvant chemoradiation had a median survival of 20 months compared to 14 months for untreated patients. Two year survival was 44% and 30% respectively. There was no survival advantage to the more intensive adjuvant therapy. A follow-up report\(^{9}\) of 616 patients found adjuvant chemoradiotherapy as a strong predictor of outcome with a hazard ratio of 0.5. Recently, combined experience of Johns Hopkins and Mayo Clinic was presented.\(^{41}\) Median overall survival in 1045 patients with resected pancreatic adenocarcinoma was higher in patients who received 5-FU based chemoradiation than those on observation alone (22.5 months versus 16.3 months).

**VIRGINIA MASON CLINIC EXPERIENCE**\(^{42}\): This centre conducted a phase II trial in 1995, producing data with highest seen survival after adjuvant therapy for pancreatic cancer. Results from 43/53 enrolled patients on this study were published in 2003. Eighty six percent of patients had stage III disease, 19% had positive margins and 84 % had positive lymph nodes. These patients were treated with EBRT to 50 Gy with concurrent chemotherapy with 5-FU 200mg/m\(^2\)/day continuous infusion, cisplatinum 30 mg/m\(^2\) weekly, and interferon-\(\alpha\) 3 million units subcutaneously every alternate day. After completion of chemoradiation, patients received 5-FU 200mg/m\(^2\)/day continuous infusion on weeks 10 through 15 and 18 through 23. With a median follow-up of 4 years, the median survival, 1-year survival, 2-year overall survival and 5-year overall survival were 44 months, 90%, 58% and 45%, respectively. With these encouraging data came significant toxicity, with 70% of patients experiencing grade III toxicities, and 42% of patients requiring hospitalization. The American College of Surgeons Oncology Group opened a larger, multicentre, II trial of 100 patients to further investigate this regimen, but this study closed secondary to poor accrual.
Toxicity has been an important reason for radiation falling out of favor in pancreatic cancer. The fear is justified to a certain extent due to the presence of vital structures in close proximity. Several trials have tried to evaluate toxicity with the use of modern radiation therapy techniques and have shown acceptable toxicity. These trials have mainly been investigational and feasibility studies but they provide a basis for further trials.

Johns Hopkins conducted a trial\(^43\) to determine the toxicity of an intensified postoperative adjuvant regimen for periampullary adenocarcinoma (pancreatic and nonpancreatic) utilizing concurrent 5-FU, leucovorin, dipyridamole, and mitomycin-C combined with split-course locoregional external beam radiotherapy to 50 Gy. This was followed by 4 cycles of the same chemotherapy as adjuvant therapy. Forty five patients were treated. There were no grade 3 or 4 non hematological toxicities and 47% grade 3 or grade 4 hematological toxicities of short duration. The median disease free survival was 17 months. This trial showed that toxicity is acceptable although the radiation schedule used was split course.

A German trial\(^44\) looked at concurrent chemoradiation with Gemcitabine and cisplatinum with 45 Gy radiation in incomplete resection of locally advanced pancreatic cancer. Median overall survival was 22.8 months and 3 yr survival was 26%. Hematological side effects were predominant and there was no grade 3 or 4 gastrointestinal toxicity. The authors concluded that chemoradiotherapy was safe and feasible. These feasibility studies should encourage the use of RT in the adjuvant setting.

**CONCLUSION**

The role of adjuvant radiation therapy for pancreatic adenocarcinoma remains ill-defined despite sound clinical rationale. Current standard of care for adjuvant radiation is largely based on the few prospective randomized clinical trials but consensus on the benefit of such therapy remains elusive because results from these trials are conflicting.\(^45\) Most of these favored adjuvant chemotherapy over chemoradiation. As highlighted in this article, all these trials were inappropriate in design and had a number of limitations especially with the delivery of radiation. Radiation therapy schedules employed were split course and the doses used were inadequate for microscopic tumor control. The technique used was parallel opposed antero-posterior portals which would have included large volumes of critical normal tissues with resultant increased toxicity. None of the trials used modern conformal radiation. It would be unfair to deny the patients of this deadly disease the benefit of an effective local therapy based on such flawed studies. Well designed prospective trials using balanced randomization, adequate stratification for known adverse prognostic factors, sufficient patient numbers to minimize type II statistical error and employing modern standardized radiotherapy arms are required before radiation is labeled as detrimental. The onus of doing so lies with the radiation oncology community.

**References:**

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