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HIGHLIGHT ARTICLE

Adjuvant Strategies for Resectable Pancreatic Cancer: Have We Made Progress?

Highlights from the "2012 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 19-21, 2012

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Summary

Substantial controversy remains regarding the optimal adjuvant treatment for patients with resectable pancreatic adenocarcinoma. Despite improvements in radiation techniques, systemic therapies, and incorporation of targeted agents, the 5-year survival rates for early stage patients remains less than 25% and the optimal adjuvant treatment approach remains unclear. Here we summarize the data presented at the 2012 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium regarding controversial issues surrounding the role, timing, and selection of patients for adjuvant chemoradiation strategies following curative resection for pancreatic adenocarcinoma. (Abstracts #301, #333, and #206).

Introduction

Pancreatic cancer is the 10th most common cancer in the US and the 4th leading cause of cancer deaths with over 37,500 patients dying of the disease annually [1]. Survival for patients with pancreas cancer is correlated to stage and only approximately 20% of patients present with localized disease amenable to potentially curative resection. Unfortunately, the 5-year survival rate for early stage patients remains less than 25% [1, 2, 3]. Improvements in short-term surgical outcomes have failed to demonstrate benefit and more extensive lymph node dissections in attempt to improve outcome result in higher surgical complication rate [4]. Approximately 75% of recurrences occur locally in the tumor bed or locoregionally in the abdominal cavity, with simultaneous distant failure in 50-80% of cases [3, 5, 6].

The relative value of the addition of adjuvant radiation to chemotherapy is the issue of some debate as mixed data regarding adjuvant therapy for patients with early stage pancreas cancer. Current accepted standard of care is adjuvant gemcitabine following curative resection, but there have been no conclusions regarding the role or timing of adjuvant chemoradiation. Although systemic disease represents the major risk for failure following resection, there are patients who would benefit from adjuvant local therapy that remain difficult to identify at present. A retrospective analysis of over 1,000 patients was performed to evaluate the role of adjuvant chemoradiation using modern radiotherapy techniques and concurrent 5-fluorouracil (5-FU). Cox proportional hazard models utilizing multiple covariates demonstrated significant improvement in median survival (22.5 months *vs*. 16.3 months; P<0.001) for those receiving adjuvant chemoradiation [7]. In addition, The European Organization for Research and Treatment of Cancer (EORTC 40013) randomized phase II trial of 90 patients randomized to either 4 cycles of gemcitabine or two cycles of gemcitabine followed by chemoradiation (weekly gemcitabine and 50.4 Gy) following surgical resection demonstrated a significant improvement in first local recurrence for patients receiving radiation (24% *vs*. 11%) [8]. Although gemcitabine-based chemoradiation was well tolerated, overall and disease free survival was similar for both arms [8]. As improvements in systemic therapy evolve, the importance of local control will increase and these data have revived an interest in exploring the use of radiation in the adjuvant setting. Currently, Radiation Therapy Oncology Group (RTOG 0848 [9])

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randomizes patients following surgical resection for pancreatic head adenocarcinoma to: 1) gemcitabine alone; or 2) gemcitabine plus erlotinib. Patients without evidence of progression are then randomized to: 1) one month of additional chemotherapy; or 2) one month of additional chemotherapy followed by chemoradiation with concurrent 5-FU or capecitabine.

Several investigators continue to investigate adjuvant treatment regimens in attempt to improve outcome for patients with resectable adenocarcinoma of the pancreas. At the 2012 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, controversial topics surrounding the role, patient selection, and timing of adjuvant treatment strategies following curative resection for pancreatic adenocarcinoma were presented and are summarized.

Update from the 2012 ASCO GI Cancers Symposium

The first abstract examines whether the timing of adjuvant chemoradiation influences outcome of patients undergoing curative resection for pancreatic adenocarcinoma.

Immediate versus Delayed Adjuvant Chemoradiation for Resected Pancreatic Cancer: An Analysis of Local Control and Survival. (Abstract #301 [10])

Investigators from the Massachusetts General Hospital and Brigham and Women's Hospital/Dana-Farber Cancer Institute investigated the patterns of failure and outcomes for patients treated with immediate *vs*. delayed chemoradiation following curative resection for pancreatic cancer. In this retrospective review, records were reviewed from 174 patients who underwent pancreaticoduodenectomy followed by adjuvant chemoradiation utilizing 50.4 Gy and concurrent 5-FU or capecitabine. Patients were identified as receiving immediate *vs*. delayed chemoradiation, defined as receiving any chemotherapy prior to chemoradiation. Local recurrence, progression-free and overall survivals were determined for each group and results were compared using a log-rank test. Seventy-one percent (123 patients) received immediate chemoradiation, of whom 101 (82%) received additional chemotherapy (5-FU or gemcitabine). The remaining 51 patients (29%) received delayed chemoradiation preceded by a median of 4 cycles of gemcitabine.

Twelve percent (6/51) patients in the delayed chemoradiation group experienced local recurrence prior to initiation of chemoradiation. At a median follow-up period of 33 months, 49% (25/51) of patients in the delayed chemoradiation group had local recurrence *vs*. 28% (35/124) in the immediate chemoradiation cohort with 1-year local recurrence rates of 40% and 18%, respectively (P=0.0093). There was no significant difference in progression-free survival (12.8 months *vs*. 12.2 months) or overall survival (24.8 months *vs*. 26.7 months) between immediate or delayed chemoradiation. The authors concluded that delayed radiation is associated with an increased risk of local recurrence, though this did not appear to impact progression-free or overall survival [10].

Despite a significant difference in local recurrence rates between immediate and delayed chemoradiation, progression-free and overall survivals were not affected. The lack of a progression-free or overall survival benefit is likely due to the effect of distant failures, although distant relapse rates were not reported in this abstract. Distant failure following surgery remains a significant problem for the majority of resectable pancreatic cancers making it difficult to determine the relative importance of local control on outcome.

Investigators have attempted to address the problem of distant failure by improving systemic therapy, including the development of more active regimens and/or protracted chemotherapy schedules. The original Gastrointestinal Tumor Study Group Trial demonstrated a survival benefit with the incorporation of postoperative 5-FU-based chemoradiation regimen compared to surgery alone. This adjuvant regimen included weekly 5-FU for 2 years or until disease progression [11, 12]. Maintenance chemotherapy has not been routinely incorporated into modern trials which have resulted in conflicting data regarding the benefit of adjuvant chemoradiation *vs*. chemotherapy alone. The authors of the following abstract examine this issue.

Maintenance Therapy with Capecitabine in Patients with Resected Pancreatic Adenocarcinoma After Adjuvant Therapy. (Abstract #333 [13])

The group from Georgetown University investigated whether maintenance chemotherapy following chemoradiation would further improve patient outcome in a single institution retrospective review that reports survival data for patients who were treated with curative surgery, standard adjuvant chemotherapy with or without chemoradiation, and maintenance capecitabine. Among 214 patients who underwent resection for pancreatic adenocarcinoma since 2007, 21 (10%) received maintenance capecitabine for a median of 12.5 months, ranging from 2 months to 24 months. Sixty-five percent of patients had node positive cancers. At median follow-up of 33 months, median overall survival was promising at 48 months, with 2-year and 5-year overall survivals at 94% and 40%, respectively. The median disease free survival was 39 months, with 2-year and 5-year disease free survival of 67% and 25%, respectively. The authors concluded that capecitabine maintenance following surgery and adjuvant chemoradiation may improve overall and progression-free survival compared to historical data [13].

Maintenance chemotherapy may in fact improve survival and warrants further evaluation in prospective controlled trials; however, not all pancreatic adenocarcinomas respond to currently available

systemic therapies. It is for this reason that other investigators are exploring the use of prognostic markers to select patients who may benefit from aggressive adjuvant treatment.

An Analysis of ERCC1, hENT1, RRM1, and RRM2 Expression in Resected Pancreas Adenocarcinoma: Implications for Adjuvant Treatment. (Abstract #206 [14])

Fisher *et al*. from Emory University attempted to identify patients who may be at increased risk for recurrence by analyzing expression of a panel of proteins hypothesized to be prognostic in pancreatic cancer and other malignancies, including excision repair cross complementing gene 1 (ERCC1) [15], human equilibrative nucleotide transporter 1 (hENT1), and ribonucleotide reductase 1 and 2 (RRM1 and RRM2). In this study, a prospective database of 220 patients who underwent curative resection for adenocarcinoma of the pancreas was used to randomly select 95 patients whose tumors were analyzed for RRM1 and 2, hENT1, and ERCC1 expression using immunohistochemistry. High levels of expression of RRM1, RRM2, hENT1, and ERCC1 were demonstrated in 40%, 17%, 85%, and 16% of patients, respectively, but only RRM2 and ERCC1 were associated with statistically significant reductions in relapse-free and overall survivals. In multivariate analysis looking at other adverse prognostic factors, high RRM2 and ERCC1 remained independent negative prognosticators. In a subset analysis of 74 patients who received adjuvant therapy, high RRM2 and ERCC1 remained negative predictors of relapse-free and overall survivals. The authors concluded that RRM2 and ERCC1 may facilitate personalized treatment recommendations for adjuvant therapy [10] in the treatment of resectable pancreatic cancer.

Discussion

The prognosis for patients with pancreatic cancer remains poor and current data regarding optimal adjuvant therapy following surgery for resectable adenocarcinoma is conflicting and many of the studies are limited by design flaws. The abstracts presented at the 2012 ASCO GI Cancers Symposium attempt to provide further data regarding controversial issues associated with adjuvant treatment. These studies are limited by the retrospective design, small sample sizes, and variable treatment regimens. However, they raise important questions regarding the challenges faced in the adjuvant therapy of resectable pancreatic cancer.

Interestingly, the series from Massachusetts General Hospital and Brigham and Women's Hospital/Dana-Farber Cancer Institute demonstrated that local control is improved with immediate adjuvant chemoradiation compared to delayed chemoradiation [10]. A frequently utilized approach is to administer 2-4 cycles of systemic therapy followed by chemoradiation. By delivering full dose chemotherapy prior to chemoradiation, it allows an attempt at treating micrometastatic disease early and potentially identifies patients with resistant disease who may progress systemically or locally despite local control measures. As it stands, local control does not have significant impact on patient survival outcomes, but it does play an important role in patient quality of life, as local recurrences are fraught with patient morbidity. Improvement in distant failure rates will allow greater scrutiny of the importance of local control on patient survival outcomes. Improvements in patient selection may identify a subset of patients undergoing curative resection in which improvements in local control can be associated with a survival benefit.

While the idea of maintenance chemotherapy is intriguing, the conclusions drawn by the Georgetown group are severely limited by the small sample size, large range of maintenance duration, and unclear effects on distant and local control given that only a subset of patients received adjuvant chemoradiation. Some investigators have speculated that survival benefit associated with the use of maintenance chemotherapy, and not chemoradiation as prolonged exposure to therapy, could potentially maintain pressure on dormant cancer cells that remain in G0 arrest, by attacking them as they infrequently enter G1/S. Although these data are intriguing, they do not provide a level of evidence to support any conclusion. Future data would ideally attempt to control for adjuvant local therapy prior to pursuing a prospective randomized trial investigating the impact of maintenance chemotherapy on survival.

Lastly, patient stratification and selection based on biomarkers has been a topic of interest and there are a number of investigators evaluating the potential of various marker panels in patient selection for treatment. The abstract presented by Fisher *et al.* (Abstract #206 [14]) demonstrates an association with high RRM2 and ERCC1 protein expression and patient prognosis, but fails to provide data to support the specific use of these markers for treatment selection. Further investigation is warranted to determine prognostic significance of such marker panels on patterns of failure in an attempt to identify patients who would benefit from specific types of adjuvant therapies. An improved understanding of the biology of pancreatic cancer may become more important in order to identify subsets of patients who may be at increased risk for local recurrences warranting more aggressive local therapies, or alternative systemic therapies, for prevention of distant failures. Further confirmatory studies are needed to validate the utility of any biomarker panel to optimally identify patients most at risk for local failure in this largely systemic disease and perhaps, lead to personalized treatment recommendations.

In conclusion, the data presented at the 2012 ASCO GI Cancers Symposium although intriguing, provide little concrete evidence to clarify the controversies currently associated adjuvant chemoradiation following curative surgery for resectable adenocarcinoma of the pancreas.

Conflict of interest The authors have no potential conflict of interest

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