Pancreatic cancer, the fourth most common cause of cancer deaths, has a five-year survival rate of 5% or less. Surgical removal of the tumor may improve survival, but survival remains poor even in optimally resected patients. The best adjuvant therapy for patients with resected pancreatic cancer is not clear. Surgical resection followed by chemoradiation and maintenance chemotherapy has been considered the most beneficial treatment for improving survival, but more recent studies have suggested that chemotherapy alone is more effective. The purpose of this article is to review randomized controlled studies of adjuvant chemoradiation or chemotherapy alone in the treatment of resected pancreatic cancer and to determine the optimal adjuvant therapy after curative resection with negative or microscopically positive margins. The outcomes of interest were overall survival and disease-free survival. The results indicate that chemoradiation is an acceptable option for adjuvant treatment. Three of the four randomized controlled trials suggest that adjuvant chemoradiation for resected pancreatic cancer improves overall survival. Adding gemcitabine to the chemoradiation regimen also confers increased disease-free survival. Providers counseling patients regarding treatment options for resected pancreatic cancer should continue to recommend adjuvant therapy—a combination of chemotherapy including gemcitabine and radiotherapy—for appropriately selected patients.
Literature Review

A literature review using PubMed included the terms pancreas cancer, chemotherapy, and randomized controlled trials. The literature includes several small, single-institution, nonrandomized studies and some randomized controlled trials studying the efficacy of adjuvant therapy for resected pancreatic cancer. The intention of the literature review was to determine evidence-based practice recommendations based only on randomized controlled studies. One exception is the GITSG (1987) adjuvant study, which was a nonrandomized confirmatory study of the previous randomized study by Kalser & Ellenberg (1985). The studies reviewed all enrolled patients who had undergone potentially curative resection before receiving adjuvant therapy or being followed up with observation. These trials evaluated the use of several different treatment regimens—chemotherapy alone, chemoradiation, standard 5-FU chemoradiation with or without gemcitabine, gemcitabine chemotherapy alone, and observation after surgery in various different combinations.

Gastrointestinal Tumor Study Group 9173 Trial

Kalser & Ellenberg (1985) aimed to determine the value of postoperative adjuvant radiotherapy combined with 5-FU chemotherapy versus no postoperative adjuvant treatment for resected adenocarcinoma of the pancreas. They randomly assigned 43 patients, with 21 patients receiving treatment and 22 patients in the control group. The treatment arm consisted of two courses of radiotherapy to a dose of 20 Gy for each course separated by a two-week break. Bolus 5-FU chemotherapy was given on the first three days at the start of each course of radiotherapy. After radiotherapy, the protocol called for weekly 5-FU chemotherapy for two years or until recurrent disease was found. However, only a small percentage of patients received the maintenance chemotherapy.

Results and Limitations

Survival was prolonged for the patients who underwent resection of pancreatic cancer followed by adjuvant therapy using chemoradiation (see Table 1). The median survival was 20 months, compared with 11 months in the control group. The survival advantage using adjuvant chemoradiation followed by maintenance chemotherapy was statistically significant. Other important findings from the study were that the participants' Eastern Cooperative Oncology Group performance status and extent of tumor at the time of surgery were strong predictors of overall survival (Chu et al., 2003; Garofalo et al., 2006; Kalser & Ellenberg, 1985).

The study had some limitations, including its small sample size. Patients were accrued for approximately eight years and quality assurance was inadequate in maintaining study parameters. For instance, five of the patients began treatment after the stated protocol time limit of 4–10 weeks after surgery. In addition, six participants did not receive the appropriate radiotherapy, and maintenance chemotherapy was administered for two years to only two of the patients. Critics of the study also claim that selection bias occurred because participants who recovered promptly from surgery had a higher likelihood of being enrolled in the study. A good performance status does improve outcome, and if poor performers were excluded, the results could be skewed (Chu et al., 2003; Kalser & Ellenberg, 1985).

Relevance of the Study

Patients who received postoperative chemoradiation had improved survival. This form of therapy should be considered when making treatment recommendations for patients with resected pancreatic cancer.

Adjuvant Gastrointestinal Tumor Study Group Trial

The GITSG (1987) study, which aimed to confirm the results of the GITSG 9173 trial (Kalser & Ellenberg, 1985), was not randomized. Instead, the trial registered an additional 30 patients to receive the same treatment regimen administered by Kalser...
<table>
<thead>
<tr>
<th>TRIAL</th>
<th>AUTHORS</th>
<th>ADJUVANT THERAPY</th>
<th>N</th>
<th>MEDIAN SURVIVAL (MONTHS)</th>
<th>MEDIAN DFS (MONTHS)</th>
<th>ESTIMATED FIVE-YEAR SURVIVAL (%)</th>
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<tr>
<td>GITSG 9173</td>
<td>Kalser &amp; Ellenberg, 1985</td>
<td>RT/CT: 20 Gy over two weeks plus bolus 5-FU; two-week break; 20 Gy over two weeks plus bolus 5-FU</td>
<td>2</td>
<td>20.0</td>
<td>11.0</td>
<td>18</td>
<td>0.04</td>
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<td>No adjuvant therapy</td>
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<td>Adjuvant GITSG</td>
<td>GITSG, 1987</td>
<td>RT/CT: 20 Gy over two weeks plus bolus 5-FU; two-week break; 20 Gy over two weeks plus bolus 5-FU</td>
<td>30</td>
<td>18.0</td>
<td>–</td>
<td>20</td>
<td>–</td>
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<td>EORTC Phase III</td>
<td>Klinkenbijl et al., 1999</td>
<td>RT/CT: 20 Gy over two weeks plus CI 5-FU; two-week break; 20 Gy over two weeks plus CI 5-FU</td>
<td>104</td>
<td>24.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>28&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.10&lt;sup&gt;h&lt;/sup&gt;</td>
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<td>19.0&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>22&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>ESPAC-1</td>
<td>Neoptolemos et al., 2004</td>
<td>CT: five days of bolus leucovorin and bolus 5-FU every 28 days for six cycles</td>
<td>75</td>
<td>21.6</td>
<td>29</td>
<td></td>
<td>0.05 (RT/CT, RT/CT and CT versus CT, no RT/CT)</td>
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<td>RT/CT: 20 Gy over two weeks plus bolus 5-FU; two-week break; 20 Gy over two weeks plus bolus 5-FU, five days of bolus 5-FU every 28 days for 6 cycles</td>
<td>72</td>
<td>19.9</td>
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<td>0.009 (CT, RT/CT and CT versus RT/CT, no RT/CT)</td>
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<td>RT/CT and CT: 20 Gy over two weeks plus bolus 5-FU; two-week break; 20 Gy over two weeks plus bolus 5-FU</td>
<td>73</td>
<td>13.9</td>
<td>7</td>
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<td>16.9</td>
<td>11</td>
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<tr>
<td>Intergroup RTOG 9704</td>
<td>Regine et al., 2006</td>
<td>RT/CT (5-FU): 5-FU for 21 days; 5-FU plus RT; 5-FU for three months</td>
<td>221</td>
<td>16.7</td>
<td>21&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>RT/CT (gemcitabine): gemcitabine weekly for three weeks; 5-FU plus RT; gemcitabine for three months</td>
<td>221</td>
<td>18.8</td>
<td>31&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>–</td>
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<tr>
<td>CONKO Phase III</td>
<td>Oettle et al., 2007</td>
<td>CT: six cycles of gemcitabine</td>
<td>179</td>
<td>22.1</td>
<td>13.4</td>
<td>18</td>
<td>&lt; 0.001&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>Observation</td>
<td>175</td>
<td>20.2</td>
<td>6.9</td>
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<td>&lt; 0.06&lt;sup&gt;g&lt;/sup&gt;</td>
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<sup>a</sup>Stated only as “similar” to the previous trial
<sup>b</sup>These results are based on the two-sided log-rank test and not on the reanalysis using a one-sided log-rank test.
<sup>c</sup>Results for patients with pancreatic cancer only; differences were not significant.
<sup>d</sup>These results are based on the reanalysis using the one-sided log-rank test.
<sup>e</sup>Estimated three-year survival
<sup>f</sup>Median disease-free survival
<sup>g</sup>Overall survival

5-FU—5-fluorouracil; CI—continuous infusion; CT—chemotherapy; DFS—disease-free survival; EORTC—European Organisation for Research and Treatment of Cancer; ESPAC—European Study Group for Pancreatic Cancer; GITSG—Gastrointestinal Tumor Study Group; RT—radiation therapy; RTOG—Radiation Therapy Oncology Group
and Ellenberg (1985). No control group was used for comparison because of the significant findings of the previous study.

**Results and Limitations**

In the GITSG confirmatory trial, the new cohort of 30 patients had similar results as those in the previous trial, along with improved survival. The median survival was 18 months. One notable difference between the two studies was that the patients in this study had a better overall performance status than those in the previous study. This study continued to validate that the participants’ Eastern Cooperative Oncology Group performance status was a strong predictor of overall survival (Chu et al., 2003; GITSG, 1987).

A limitation of the study was that it did not have a control arm for comparison, and participants were not assigned randomly to treatment. The performance status of the participants before study enrollment was better than that of all patients in the initial study. The superior performance status of the participants in the study may have influenced the improved outcome seen with treatment (Chu et al., 2003; GITSG, 1987).

**Relevance of the Study**

Patients receiving postoperative chemoradiation had improved survival as compared with patients not receiving treatment in the initial study. Performance status should be considered when making recommendations for adjuvant treatment. Chemoradiation should be recommended for patients with resected pancreatic cancer.

**European Organisation for Research and Treatment of Cancer Phase III Trial**

Klinkenbijl et al. (1999) sought to determine whether surgical resection along with adjuvant radiotherapy and 5-FU resulted in a survival benefit versus observation after surgery. This randomized controlled study included 29 institutions across Europe. Patients had head of pancreas cancer (n = 114) or periampullary cancers (n = 104). Patients were included if they were able to start treatment within eight weeks of surgical resection of the tumor; after surgery, 108 patients were randomly assigned to the observation after surgery group, and 110 were assigned to the treatment group. Six participants in the treatment group and five participants in the observation arm were deemed ineligible. The adjuvant treatment was similar to that in the GITSG trials, except that maintenance chemotherapy was not administered after chemoradiation. The chemotherapy regimen given (started the same day as radiotherapy) was continuous-infusion 5-FU, as opposed to a bolus dose used in the GITSG studies. Radiotherapy was administered daily over two weeks to a dose of 20 Gy. After a two-week break, an additional 20 Gy was given over two weeks for a total dose of 40 Gy (Garofalo et al., 2006; Klinkenbijl et al., 1999).

**Results and Limitations**

The treatment regimen in the study did not show an advantage in disease-free survival or overall survival. The authors concluded that adjuvant chemoradiation was not justified for use as a standard treatment in patients with resected pancreatic and periampullary cancer because of its limited benefit on overall survival. Evaluation of only the patients with resected pancreatic cancer in the study showed that the patients undergoing treatment had slightly improved survival versus those in the observation after surgery arm, but this was not statistically significant (Klinkenbijl et al., 1999; Chu et al., 2003).

Pancreatic and periampullary tumors were included in this study. In general, periampullary tumors have a more favorable overall survival rate, but no benefit was observed in the study. Although a subset analysis of the patients with pancreatic cancer did show slight improvement in overall survival, it was not statistically significant. Inclusion of both tumor types did not allow for adequate numbers of patients with pancreatic cancer for evaluation. The inadequate sample size of patients with pancreatic cancer would argue against drawing additional treatment conclusions for this group (Chu et al., 2003).

Garofalo et al. (2006) questioned the method used for statistical analysis in the study. They considered the two-sided log-rank test to be used inappropriately because the treatment arm was being examined for benefit as opposed to harm over the control arm. Reanalysis of the study data using a one-sided log-rank test showed that the difference between study arms in overall survival for patients with pancreatic cancer at two years would have reached statistical significance.

**Relevance of the Study**

The assumption based on statistical reanalysis is that patients with pancreatic cancer who receive postoperative chemoradiation have improved survival; therefore, it should be considered part of the standard of care provided for these patients.

**European Study Group for Pancreatic Cancer Trial**

Neoptolemos et al. (2004) conducted a multicenter trial as part of the ESPAC investigations. This group sought to determine the benefits of adjuvant therapy by comparing adjuvant chemotherapy alone, adjuvant chemoradiation with or without maintenance chemotherapy, and no adjuvant therapy. The study used a two-by-two factorial design and enrolled 289 participants, who were randomly assigned to one of four groups and followed up for a median of 47 months (Choti, 2004). A total of 147 patients were assigned to chemotherapy: 75 patients received chemotherapy alone and 72 patients received chemotherapy combined with chemoradiation. Another 142 patients were assigned randomly to chemoradiation (n = 73) or no adjuvant therapy (n = 69).

Chemoradiation was given over a two-week period. The radiotherapy was administered daily for two weeks to a dose of 20 Gy. After a two-week break, an additional 20 Gy was given over two weeks for a total dose of 40 Gy. Bolus 5-FU chemotherapy was given on the first three days at the start of each course of radiotherapy. The chemotherapy alone group received six cycles of bolus leucovorin and bolus 5-FU. Each chemotherapy cycle was administered on five consecutive days every 28 days. The
Results and Limitations

The studies showed that patients receiving adjuvant chemotherapy had significant survival benefit over the chemoradiation and observation after surgery groups. Also, they suggested that adjuvant chemoradiation was harmful because it decreased survival time (Choti, 2004; Chu et al., 2003; Neoptolemos et al., 2004).

The complexity of the study design made interpreting the findings difficult. The purpose of the design was to allow analysis of the effect of each therapy on survival and possible interaction between the treatments. Because chemoradiation and chemotherapy were given consecutively, one treatment could have affected compliance to the subsequent chemotherapy regimen because of the toxic effects of the previous treatment. Some believe that the study was underpowered for the type of analysis used. Differences in radiation doses given by the various centers was another criticism of this study (Bergenfeldt & Albertsson, 2006; Choti, 2004; Chu et al., 2003).

Another criticism of the study was that the chemoradiation group started chemotherapy at a mean of 48 days after surgery, but the chemoradiation groups started treatment at a mean of 91 days after surgery. The concern is whether patients in the chemoradiation group started treatment later because of poorer performance status (Bergenfeldt & Albertsson, 2006). In addition, participants were not precluded from enrollment in the study even if they had prior chemotherapy and radiotherapy. Some of the participants in the group without chemotherapy actually had received chemoradiation previously (Regine & Abrams, 2006). The no adjuvant therapy group in the study had improved survival, which was unlikely to be related to surgery alone. The finding may be related to better postoperative care or better performance status of the patients. The no adjuvant therapy group in the study had improved survival in relation to past studies. The better-than-average survival rate may have contributed to the chemoradiation arm appearing worse (Choti, 2004; Chu et al., 2003; Regine & Abrams).

Relevance of the Study

The results of the study suggest an overall survival benefit with adjuvant chemotherapy but a detrimental effect with the use of adjuvant chemoradiation causing decreased survival. Chemotherapy should still be considered as an adjuvant treatment. Patients who received postoperative chemotherapy had improved survival; therefore, postoperative chemotherapy should be considered as part of the standard of care provided for patients with resected pancreatic cancer.

Intergroup Radiation Therapy Oncology Group 9704 Trial

This intergroup trial by RTOG aimed to evaluate the addition of postoperative gemcitabine chemotherapy to the adjuvant 5-FU-based chemoradiation and its effect on survival for patients with resected pancreatic cancer. The trial is different from other trials reviewed in that RTOG considers adjuvant chemoradiation the standard of care for patients with resected pancreatic cancer, which is why the trial did not include an observation arm. A total of 538 participants were enrolled in the study, but only 442 were eligible for assessment. One treatment arm gave the traditional 5-FU-based chemotherapy for 21 days followed by 5-FU and radiotherapy to 221 patients. Patients then received 5-FU chemotherapy for three months. The second arm of the study administered gemcitabine once a week for three weeks followed by 5-FU and radiotherapy to 221 participants. Patients then received gemcitabine chemotherapy for three months (Regine & Abrams, 2006; Regine et al., 2006).

Results and Limitations

Data from the study indicate that the addition of gemcitabine chemotherapy to 5-FU chemoradiation increases the median survival and the percentage of three-year survival as compared with 5-FU chemotherapy alone (Regine & Abrams, 2006; Regine et al., 2006). The complete study data have yet to be published, so appropriate peer review of the study is lacking. The trial cannot be compared directly with the preceding trials because its main purpose was to evaluate the addition of gemcitabine chemotherapy to the current standard of care with chemoradiation.

Relevance of the Study

The preliminary results are positive, with data showing improved survival. Chemoradiation plus additional gemcitabine chemotherapy should be considered when giving treatment recommendations regarding adjuvant therapy for patients with resected pancreatic cancer. Chemoradiation including gemcitabine should be considered as the standard of care provided for these patients.

Charité Onkologie Phase III Trial

This randomized controlled phase III trial by Oettle et al. (2007) was a multi-institutional collaboration in Austria and Germany. The purpose of the CONKO trial was to determine whether adjuvant chemotherapy using gemcitabine after complete surgical resection of pancreatic cancer would increase disease-free survival for six months or more. The CONKO trial recruited a total of 368 patients who were randomly assigned to the gemcitabine therapy group (n = 186) or the observation group (n = 182) after resection (R0 and R1). Because of study entrance criteria violations, 14 patients (seven from each arm) were excluded from the trial.
Results and Limitations

Results of the trial showed significantly improved disease-free survival for the patients using adjuvant gemcitabine after R0 and R1 resection, as compared with the observation group (Oettle et al., 2007). A limitation of the study is that the surgical resection and staging of patients was not validated across the institutions or reviewed independently.

Relevance of the Study

The improved disease-free survival shown in the study, combined with the positive results of the RTOG 9704 trial, indicates that gemcitabine chemotherapy does confer benefit when used as adjuvant treatment. Gemcitabine should be incorporated into the standard of care for adjuvant treatment of patients with resected pancreatic cancer.

Evidence for Recommendations

The National Comprehensive Cancer Network (NCCN, 2008) provides a guideline for treatment recommendations for pancreatic adenocarcinoma. The guidelines point to the conflicting evidence shown by the studies reviewed in this article. Because the studies suggesting that chemoradiation was not beneficial or was even detrimental have been highly criticized, panel members recommended not changing the previous standard of care using chemoradiation. The opinion of the NCCN Pancreatic Adenocarcinoma Panel members was that chemoradiation is an acceptable option for adjuvant treatment. In addition, three of the four randomized controlled studies reviewed in this article, along with the GITSG (1987) confirmatory study, indicate that adjuvant chemoradiation for patients with resected pancreatic cancer improves overall survival (Choti, 2004; Chu et al., 2003; Garofalo et al., 2006; GITSG; Kalser & Ellenberg, 1985; NCCN; Regine & Abrams, 2006; Regine et al., 2006). Adding gemcitabine chemotherapy to the chemoradiation regimen also confers a benefit for disease-free survival (Oettle et al., 2007).

Additional evidence for using adjuvant chemoradiation in resected pancreatic cancer is provided in other large single-institution studies; however, these studies are not randomized. Corsini et al. (2007) conducted a retrospective review of 472 patients with pancreatic cancer who underwent resection, with negative surgical margins and adjuvant chemoradiation, at the Mayo Clinic from 1975–2005. The retrospective analysis found that the addition of postoperative adjuvant chemoradiation significantly improves overall survival. Median survival for patients with resected pancreatic cancer receiving adjuvant treatment was 25.2 months, versus 19.2 months for patients who had surgery without adjuvant treatment (p = 0.001). Swartz et al. (2006) also conducted a large retrospective review of patients who received postoperative adjuvant chemoradiation for pancreatic cancer at Johns Hopkins Hospital. The study showed significantly improved overall survival for patients who received adjuvant chemoradiation after pancreaticoduodenectomy for localized pancreatic cancer as compared with those who received pancreaticoduodenectomy alone. Median survival for adjuvantly treated patients with resected pancreatic cancer was 20.8 months, versus 13 months for patients who had surgery alone. These two retrospective studies support the results of the randomized studies reviewed in this article. These two studies are large homogeneous studies. However, they are not randomized trials, which creates concern for the possibility of selection bias. The evidence from these retrospective studies suggests that postoperative chemoradiation improves survival.

Recommendations for Practice and Nursing Considerations

Physicians, nurse practitioners, physician assistants, clinical nurse specialists, and registered nurses counseling patients regarding treatment options for resected pancreatic cancer can provide education about treatment recommendations based on the evidence presented in this article. Providers should continue to recommend adjuvant therapy for appropriately selected patients, with a combination of chemotherapy including gemcitabine and chemoradiation (typically 5-FU administered during radiotherapy). The weight of evidence, provided by the randomized controlled studies, the confirmatory study reviewed in this article, and the large nonrandomized studies cited continue to support the use of chemoradiation as the optimal standard of care. Although adjuvant chemoradiation improves survival, nurses should remember that patients with pancreatic cancer have a poor prognosis.

Nurses providing care for patients with pancreatic cancer need to be cognizant that the recommendations noted in this article are based on patients with surgically resected cancer and either negative surgical margins (R0) or microscopically positive surgical margins (R1). These patients have early-stage disease. Approximately 10%–15% of patients with pancreatic cancer have resectable, early-stage disease. Other treatment recommendations would be considered for patients with higher-stage disease. Halls & Ward-Smith (2007) provide a succinct general overview to educate nurses and other providers about the screening and detection of pancreatic cancer and treatments available.

In summary, patients with early-stage pancreatic cancer should undergo surgery. Following surgery, these patients should be consulted regarding postoperative adjuvant chemoradiation.

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References


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