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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Pancreatic Adenocarcinoma
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Pancreatic Adenocarcinoma

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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Pancreatic Adenocarcinoma, Version 1.2019

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Pancreatic Adenocarcinoma discuss the diagnosis and management of adenocarcinomas of the exocrine pancreas and are intended to assist with clinical decision-making. These NCCN Guidelines Insights discuss important updates to the 2019 version of the guidelines, focusing on postoperative adjuvant treatment of patients with pancreatic cancers.

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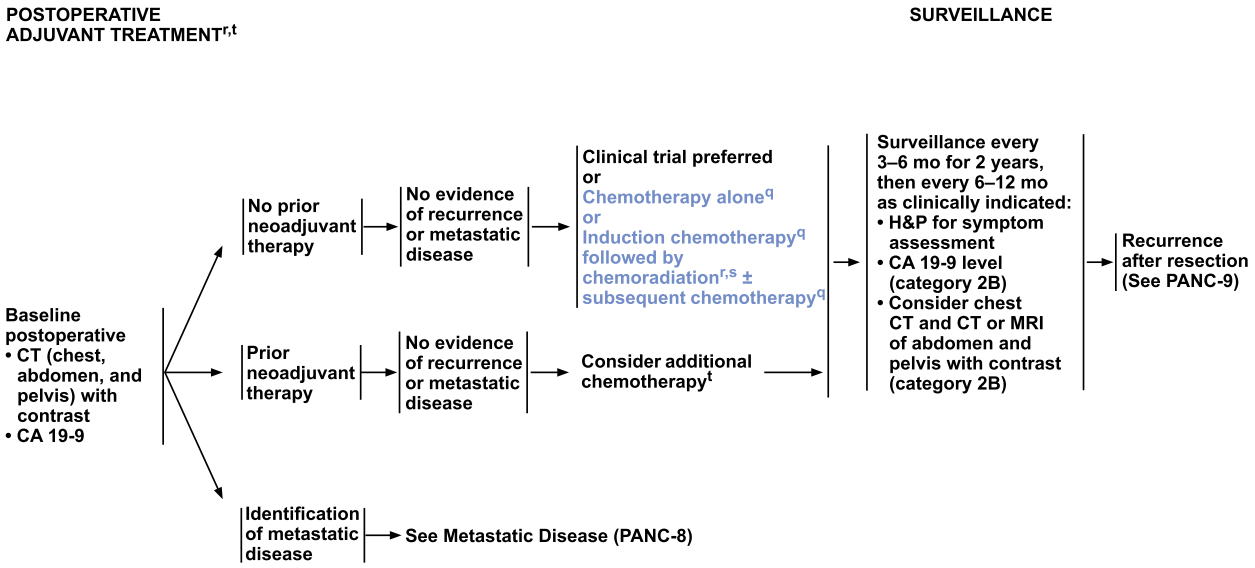

[q]See Principles of Chemotherapy (PANC-F).
[r]Adjuvant treatment should be administered to patients who have adequately recovered from surgery; treatment should be initiated within 12 weeks. If systemic chemotherapy precedes chemoradiation, restaging with imaging should be done after each treatment modality.
[s]See Principles of Radiation Therapy (PANC-G).
[t]Patients who have received neoadjuvant chemoradiation or chemotherapy may be candidates for additional chemotherapy following surgery and multidisciplinary review. The adjuvant therapy options are dependent on the response to neoadjuvant therapy and other clinical considerations.

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PANC-5

Overview

In 2019, an estimated 56,770 people in the United States will be diagnosed with pancreatic cancer and approximately 45,750 will die of the disease.[1] Pancreatic cancer is the fourth most common cause of cancer-related death among US men (after lung, prostate, and colorectal cancers) and women (after lung, breast, and colorectal cancers).[1] From 1999 to 2008, the incidence of pancreatic cancer increased in the United States, likely due to the increasing prevalence of obesity, an aging population, and other unknown factors.[2–4] Mortality rates for pancreatic adenocarcinoma (PAC) have remained largely unchanged,[5,6] although a recent SEER-based study of the past 40 years showed decreased incidence-based mortality from 2012 to 2014.[7]

Goals of surgery for PAC include oncologic resection of the primary tumor and regional lymph nodes. Although surgical resection is the only potentially curative technique for managing pancreatic cancer, only 15% to 20% of patients are eligible for this procedure.[8] Even with negative margins (R0 resections), recurrence rates are very high. Therefore, additional therapy is required for all patients with resected PAC (see PANC-5, above). The standard approach to therapy in patients with resectable disease has been postoperative treatment. Currently, it is estimated that only approximately half of patients with potentially curative resections receive adjuvant therapy due to issues associated with postoperative complications, recovery, and performance status.[9] Median survival for patients with resected tumors under optimal clinical trial conditions after adjuvant therapy have typically ranged from 20.1 to 28.0 months,[10–14] although results from a recent study extended this to 54.4 months.[15]

An emerging approach to perioperative treatment is neoadjuvant therapy for patients with borderline resectable disease, who are at higher risk for R1 resections, and patients with resectable disease, especially in those with high-risk features.[16] One of the putative benefits of neoadjuvant therapy includes increasing the likelihood that a higher proportion of patients with resectable disease will receive chemotherapy and/or radiation therapy (RT).[17] Current research focuses on determining the most effective approach for treating resectable PAC, and ongoing studies are comparing neoadjuvant plus adjuvant therapy versus adjuvant therapy alone. Recent retrospective data[18–21] show improved survival in patients who

PRINCIPLES OF CHEMOTHERAPY

Adjuvant Therapy

- The CONKO 001 trial demonstrated significant improvements in disease-free survival and overall survival with use of postoperative gemcitabine as adjuvant chemotherapy versus observation in resectable pancreatic adenocarcinoma.[1]
- ESPAC-3 study results showed no significant difference in overall survival between 5-FU/leucovorin versus gemcitabine following surgery. When the groups receiving adjuvant 5-FU/leucovorin and adjuvant gemcitabine were compared, median survival was 23.0 months and 23.6 months, respectively.[2]
- Data from ESPAC-4 support the use of gemcitabine combined with capecitabine (1,660 mg/m^2/d d1–21 q 4 weeks) with superiority demonstrated compared to gemcitabine alone (HR, 0.82; 95% CI, 0.68, 0.98; P = .032).[3]
- No significant differences were observed in the RTOG 97-04 study comparing pre- and post-chemoradiation 5-FU with pre- and post-chemoradiation gemcitabine for postoperative adjuvant treatment.[4]
- Recommended adjuvant therapy options apply to patients who did not receive prior neoadjuvant therapy. For those who received prior neoadjuvant therapy, the adjuvant therapy options are dependent on the response to neoadjuvant therapy and other clinical considerations.

Preferred Regimens	Other Recommended Regimens
• Gemcitabine + capecitabine (category 1) • Modified FOLFIRINOX (category 1)[a]	• Gemcitabine (category 1) • 5-FU/leucovorin (category 1) • CI 5-FU • Capecitabine (category 2B) • Induction chemotherapy (gemcitabine, 5-FU/leucovorin, or CI 5-FU) followed by chemoradiation[b] • Induction chemotherapy (gemcitabine, 5-FU/leucovorin, or CI 5-FU) followed by chemoradiation[b] followed by subsequent chemotherapy:[4] ‣ Gemcitabine followed by chemoradiation[b] followed by gemcitabine ‣ Bolus 5-FU/leucovorin followed by chemoradiation[b] followed by bolus 5-FU/leucovorin ‣ CI 5-FU followed by chemoradiation[b] followed by CI 5-FU

[a]FOLFIRINOX/modified FOLFIRINOX should be limited to those with ECOG 0-1.
[b]See Chemoradiation (PANC-F, 6 of 7).

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received neoadjuvant therapy. Additionally, some exciting new randomized trials (eg, SWOG 1505 [ClinicalTrials.gov NCT02562716] and PREOPANC-1[22]) coming to fruition will add to the understanding of this disease and the impact of neoadjuvant treatment going forward. Patients who have received neoadjuvant chemoradiation (CRT) or chemotherapy may be candidates for additional chemotherapy after surgery and multidisciplinary review. Adjuvant therapy options are dependent on the response to neoadjuvant therapy and other clinical considerations.

These NCCN Guidelines Insights highlight postoperative adjuvant treatment recommendations for patients with PAC who have not received neoadjuvant therapy, including the addition of modified FOLFIRINOX (mFOLFIRINOX) as a preferred adjuvant treatment option. For a list of all 2019 updates, see the complete version of these guidelines (available at NCCN.org). The NCCN Guidelines for PAC address all aspects of diagnosis and disease management.

Postoperative (Adjuvant) Therapy

Many chemotherapies used in the adjuvant setting were adapted from systemic therapy approaches to treat locally advanced or metastatic disease. RT and CRT sometimes are also used for pancreatic cancer in the resectable and adjuvant settings due to their potential to decrease the likelihood of local recurrence. In patients with pancreatic cancer, RT is usually given concurrently with gemcitabine- or fluoropyrimidine-based chemotherapy; chemotherapy is used as a radiosensitizer, increasing the toxicity of radiation to tumor cells.

Adjuvant CRT

In 1985, the Gastrointestinal Tumor Study Group (GITSG) initially reported that the median survival of patients undergoing pancreatoduodenectomy could be prolonged almost 2-fold by postoperative CRT.[23] This study randomly assigned patients to either observation or RT combined with an intermittent bolus of 5-fluoruracil (5-FU) after resection, weekly for a full 2 years. In addition to a prolonged median survival, CRT also resulted in a 2-year actuarial survival of 42% compared with 15% in the control group.[23]

Other studies have also shown an advantage for adjuvant CRT over observation after resection. EORTC conducted a phase III trial (N=40,891) in patients with both ampullary and pancreatic adenocarcinoma assessing adjuvant RT and 5-FU versus observation alone after

surgery. They found that the benefit of therapy was small in a subset of patients with PAC and was not statistically significant.[24] At a median follow-up of 11.7 years, no statistically significant differences were observed in the different study arms with respect to progression-free survival or overall survival (OS) for the subset of patients with PAC.[25]

In 2004, the ESPAC-1 trial conducted a large 2 × 2 factorial design trial in 289 patients with resected PAC comparing CRT alone, chemotherapy alone using 5-FU/leucovorin, CRT with chemotherapy, or observation.[10] This trial found that 5-year survival was reduced in patients treated with CRT alone compared with observation (10% vs 20%, respectively; P=.05), and was improved in patients who received chemotherapy compared with those who did not (21% vs 8%, respectively; P=.009). These results did not eliminate 5-FU–based CRT as an acceptable choice in the adjuvant setting, but did provide evidence to support adjuvant chemotherapy alone.

A more contemporary study compared different regimens incorporating CRT. The phase III RTOG 97-04 study evaluated postoperative adjuvant treatment of resected PAC using either gemcitabine or 5-FU for 3 weeks before and 12 weeks after 5-FU–based CRT for both groups.[13] This trial, which used daily fractionated RT, included prospective quality assurance of all patients, including central review of preoperative CT imaging and radiation fields.[26] Results of this study showed that, for patients with pancreatic head tumors (representing 388 of the 451 enrolled patients), there was a nonstatistically significant increase in OS in the gemcitabine arm compared with the 5-FU arm (median and 3-year survival of 20.5 months and 31% vs 16.9 months and 22%, respectively; P=.09); this benefit became more pronounced on multivariate analysis (hazard ratio [HR], 0.80; 95% CI, 0.63–1.00; P=.05). The 5-year analysis of RTOG 97-04 showed that there was in fact no difference in OS between the 2 groups, although patients with pancreatic head tumors showed a trend toward improved OS with gemcitabine (P=.08) on multivariate analysis.[27]

Benefit of Adjuvant CRT in Patient Subsets

It has been suggested that subsets of patients (eg, patients with R1 resections or positive lymph nodes) may be more likely to benefit from adjuvant CRT.

Studies that have examined R0 or R1 subsets of patients have found mixed results. For instance, patients in the ESPAC-1 trial did not derive a benefit from the addition of RT to adjuvant chemotherapy, irrespective of margin status.[28] In contrast, results from a prospectively collected database of 616 patients with resected pancreatic cancer at the Johns Hopkins Hospital found that adjuvant CRT benefited both the R0 and R1 subsets compared with observation alone.[29] The Mayo Clinic performed a retrospective review of 466 patients who had R0 resections for PAC and found an OS benefit with adjuvant CRT over observation.[30] In addition, a retrospective review of >1,200 patients with resected tumors from the Johns Hopkins Hospital and the Mayo Clinic who received adjuvant 5-FU–based CRT or were observed after resection found that CRT improved outcomes regardless of margin status (R0: relative risk [RR], 0.61; 95% CI, 0.47–0.77; P<.001; and R1: RR, 0.52; 95% CI, 0.36–0.74; P<.001).[31] A meta-analysis of 4 randomized controlled trials found evidence for an increased survival benefit with adjuvant CRT in the R1 subset (HR for death, 0.72; 95% CI, 0.47–1.10) over the R0 subset (HR for death, 1.19; 95% CI, 0.95–1.49).[32]

Data are still mixed but more suggestive when examining the role of CRT in patients with resected tumors and positive lymph nodes. One retrospective review compared outcomes of 94 patients who underwent distal pancreatectomy at the Johns Hopkins Hospital and either received adjuvant CRT or were observed after resection.[33] An exploratory subset analysis suggested that patients with positive lymph nodes derived greater benefit from adjuvant CRT than those with negative nodes. In addition, a meta-analysis of 4 randomized controlled adjuvant trials found that CRT had a similar lack of benefit in patients with positive and negative lymph nodes.[34] A subset analysis from a large, multi-institutional study of 747 patients with resected pancreatic cancer that compared the role of adjuvant CRT versus surgery alone found a significant improvement in survival with CRT only in patients with lymph node–positive disease.[35]

Role of RT in Adjuvant Regimens

Most data comparing chemotherapy versus CRT in the adjuvant setting do not generally show a survival advantage for the addition of RT. Results of ESPAC-1 suggested that the addition of RT to adjuvant 5-FU chemotherapy may be unnecessary and perhaps even harmful (OS of 13.9, 21.6, and 19.9 months for CRT, chemotherapy, and chemotherapy + CRT, respectively),[10] although this trial has been criticized for lack of attention to quality control for RT, among other concerns.[36–38] A phase II study by GERCOR randomized patients to adjuvant gemcitabine or adjuvant gemcitabine-based CRT.[39] No differences were seen in OS (24.4 vs 24.3 months) or disease-free survival (DFS; 10.9 vs 11.8 months) between the groups, but with only 45 patients in each arm, no P values were reported. In addition, the multicenter, open-label, randomized phase III CapRI trial found that adjuvant CRT with 5-FU, cisplatin, and interferon alfa-2b followed by 5-FU chemotherapy provided outcomes that were no better than adjuvant treatment with 5-FU alone.[40]

A 2012 meta-analysis of 15 prospective randomized trials found that adjuvant CRT did not improve DFS, 2-year survival, or OS (odds ratio, 0.99; P=.93) compared with surgery alone, whereas adjuvant chemotherapy improved all 3 outcomes (odds ratio for OS, 1.98; P<.001).[41] A 2013 meta-analysis of 9 trials found similar results, with HRs for death compared with no adjuvant treatment of 0.62 for 5-FU (95% CI, 0.42–0.88), 0.68 for gemcitabine (95% CI, 0.44–1.07), 0.91 for CRT (95% CI, 0.55–1.46), 0.54 for CRT + 5-FU (95% CI, 0.15–1.80), and 0.44 for CRT + gemcitabine (95% CI, 0.10–1.81).[42] However, a population-based assessment of outcomes of patients in the National Cancer Database (NCDB) with pancreatic cancer resected in 1998 through 2002 found the opposite result: CRT with chemotherapy provided better OS than chemotherapy alone in a performance status–matched comparison with no adjuvant treatment (HR, 0.70; 95% CI, 0.61–0.80 vs HR, 1.04; 95% CI, 0.93–1.18).[43] A multi-institutional pooled analysis of 955 consecutive patients who had macroscopically negative margin (R0–1) resections for pancreatic cancer also supports the supposition that adjuvant CRT with chemotherapy improved survival compared with chemotherapy alone (OS, 39.9 vs 27.8 months; P<.001) or RT alone (OS, 39.9 vs 24.8 months; P<.001).[44]

More recent advances in the delivery of radiation make older studies—which often administered radiation using more antiquated techniques and dose/fractionation schedules–difficult to apply to modern day practice. RTOG 0848 is being conducted to definitively assess the role of CRT after gemcitabine monotherapy in the adjuvant setting, and has completed accrual (ClinicalTrials.gov identifier: NCT01013649). Patients without evidence of progressive disease after 5 cycles of gemcitabine-based chemotherapy are being randomized to 1 additional round of chemotherapy or 1 additional round of chemotherapy followed by CRT with capecitabine or 5-FU. The primary end point is OS, and the trial is estimated to be completed in 2020.

Adjuvant Chemotherapy

More than a decade ago, after the use of CRT was questioned in the ESPAC-1 trial[10] and gemcitabine had shown clinical benefit and a modest survival advantage over treatment with bolus 5-FU for patients with locally advanced or metastatic disease,[45] came the large phase III CONKO-001 trial.[12] In this trial, 368 patients without prior chemotherapy or RT were randomly assigned to adjuvant gemcitabine versus observation following macroscopically complete resection. An intention-to-treat analysis of the data from CONKO-001 showed that the primary end point of increased DFS was met (13.4 vs 6.9 months; log rank P<.001).[12] Final results from this study showed median OS to be improved significantly in the gemcitabine arm (22.8 vs 20.2 months; HR, 0.76; 95% CI, 0.61–0.95; P=.01),[46] and an absolute survival difference of 10.3% was observed between the groups at 5 years (20.7% vs 10.4%).[46] Based on this study, gemcitabine monotherapy has category 1 evidence supporting its use in the adjuvant setting (see PANC-F 2 of 7, page 205).

Although results of RTOG 97-04 cannot be directly compared with the results of the CONKO-001, ESPAC-1, or ESPAC-3 trials because of differences in treatment design, timing of imaging, and patient characteristics (eg, patients enrolled in CONKO-001 were more likely to be lymph node–negative and to have positive resection margins than those in RTOG 97-04, and CONKO-001 excluded patients with high postoperative CA 19-9 or CEA levels[12]), it is interesting to note that median OS in the gemcitabine arm of CONKO-001 (22.8 months), the gemcitabine-containing arm of RTOG 97-04 (20.5 months), the bolus 5-FU/leucovorin arm of ESPAC-1 (20.1 months), and the gemcitabine and 5-FU/leucovorin arms of the ESPAC-3 study (23.6 and 23.0 months) are remarkably similar.

Results of the ESPAC-4 phase III randomized trial (N=730), in which gemcitabine + capecitabine was compared with gemcitabine monotherapy in the adjuvant setting, showed that median survival was greater for patients randomized to receive the combination regimen (28.0 months), relative to those randomized to receive gemcitabine monotherapy (25.5 months; HR, 0.82; 95% CI, 0.68–0.98; P=.032).[14] This combination also has category 1 evidence supporting its use (see PANC-F 2 of 7, page 205). The CONKO-005 phase III randomized trial tested a different combination, gemcitabine + erlotinib compared with gemcitabine alone in the adjuvant setting.[47] This combination regimen did not significantly improve OS or DFS compared with gemcitabine monotherapy.

Capecitabine monotherapy is also a treatment option in the adjuvant setting (category 2B; see PANC-F 2 of 7, page 205). The NCCN panel considers capecitabine to be a reasonable alternative to 5 FU/leucovorin only in this setting as a last choice in patients for whom other options are inappropriate or unacceptable. Gemcitabine, 5 FU/leucovorin, or continuous infusion 5-FU before gemcitabine or fluoropyrimidine-based CRT is also recommended as an adjuvant treatment, with subsequent chemotherapy being an option for patients unable to receive contemporary multiagent chemotherapy regimens.

A recent retrospective analysis of data from patients in the ESPAC-3 trial found that completion of the full course of chemotherapy was an independent prognostic factor for survival, but that time to treatment initiation after surgery was not.[48] These results suggest that delaying chemotherapy until patients adequately recover

could possibly improve outcomes. The NCCN panel therefore recommends that adjuvant treatment be initiated within 12 weeks, after adequate recovery from surgery.

mFOLFIRINOX in the Adjuvant Setting

In 2018, results of the PRODIGE 24/CCTG PA.6 phase III trial (N=493; ClinicalTrials.gov identifier: NCT01526135) were presented.[49] The trial compared adjuvant chemotherapy with gemcitabine versus mFOLFIRINOX to treat R0 or R1 resected PAC in patients with good performance status (defined as WHO performance-status score ≤1).[15] The modification is removing the 5-FU bolus, only giving 5-FU as a continuous infusion, and reducing the irinotecan dose from 180 to 150 mg/m^2 to reduce toxicity. Patients were excluded from the trial if they had metastases, R2 resection, postoperative CA 19-9 levels >180 U/mL within 3 weeks of study registration, and major comorbidities, among other criteria. Median follow-up was 33.6 months (95% CI, 30.3–36.0). Median DFS was greater for mFOLFIRINOX (21.6 months; 95% CI, 17.7–27.6) compared with gemcitabine (12.8 months; 95% CI, 11.7–15.2), and median OS (54.4 vs 35.0 months, respectively) and metastasis-free survival (30.4 vs 17.7 months, respectively) were also greater for mFOLFIRINOX. Grade 3 or 4 adverse events in the mFOLFIRINOX or gemcitabine treatment arms were reported in 75.9% versus 52.9% of patients, including grade 4 in 12% of patients in each arm, with one death due to toxicity in the gemcitabine arm.

The NCCN panel discussed the results of the PRODIGE trial[48] and stressed that the study included a select population of patients. Some panel members caution to only use this treatment in patients who meet the eligibility criteria as described in the trial. Furthermore, some panel members underscored that mFOLFIRINOX is not an appropriate therapy for all patients due to toxicity issues. The panel agreed that for patients with good performance status (ECOG 0–1), mFOLFIRINOX is preferred compared with gemcitabine monotherapy. Based on the data available, the panel designated mFOLFIRINOX a category 1 recommendation in the adjuvant setting (see PANC-F 2 of 7, page 205).

NCCN Preferred and Other Recommended Regimens

In the 2019 version, the panel applied the NCCN Categories of Preference to all chemotherapy regimens in the guidelines to indicate which recommendations are considered optimal. For adjuvant therapy regimens, the interventions were separated into 2 categories: "preferred" and "other recommended." Preferred interventions in this setting, which are based on superior efficacy, safety, and evidence, and, when appropriate, affordability, are gemcitabine + capecitabine (category 1) and mFOLFIRINOX (category 1). There are no head-to-head trials directly comparing the gemcitabine + capecitabine and mFOLFIRINOX regimens; the ESPAC-4 trial[14] and the PRODIGE 24 trial[15] both used gemcitabine monotherapy in the comparator arm.

Other recommended interventions may be somewhat less efficacious, more toxic, based on less mature data, or significantly less affordable for similar outcomes. The panel categorized gemcitabine (category 1), 5-FU/leucovorin (category 1), and continuous infusion 5-FU as other recommended regimens in the adjuvant setting. Capecitabine monotherapy is also another recommended treatment option for the adjuvant setting (category 2B). The panel considers capecitabine to be a reasonable alternative to 5-FU/leucovorin only in this setting as a last choice in patients for whom other options are inappropriate or unacceptable. Gemcitabine, 5-FU/leucovorin, or continuous infusion 5-FU before gemcitabine- or fluoropyrimidine-based CRT is also recommended as an adjuvant treatment, with subsequent chemotherapy as an option. CRT was discussed as a good option for patients with positive margins after induction chemotherapy; however, to date, no studies have demonstrated superiority of giving CRT before versus after chemotherapy in the adjuvant setting, and no studies have demonstrated benefit of CRT in addition to contemporary multiagent chemotherapy, such as gemcitabine + capecitabine or FOLFIRINOX/mFOLFIRINOX. Regardless of the therapy being considered, it is important to evaluate for extent of disease prior to therapy, because some patients experience early recurrence within the first few weeks after surgery. In addition, the panel recommends restaging a patient with imaging after systemic chemotherapy if CRT is planned.

Conclusions

Even though only a minority of patients with pancreatic cancer will be eligible for potentially curative resection, results of many trials have shown that adjuvant therapy improves outcomes over observation after resection. More options with high-level evidence are now available in this setting that are extending the median survival ranges. For the 2019 update, to help guide optimal use of adjuvant therapies, the panel members assigned NCCN Categories of Preference to the systemic therapy regimens recommended in the guidelines.

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