TABLE 112-2 SELECTED PHASE III STUDIES EVALUATING CHEMOTHERAPY TREATMENT IN ADVANCED PANCREATIC CANCER

Study	Comparator Arm	No. of Patients	Survival	
			PFS (months)	Median Survival (months)
Moore et al: J Clin Oncol 26:1960, 2007	Gemcitabine vs gemcitabine + erlotinib	569	3.55 vs 3.75 (HR 0.77; 95% CI 0.64–0.92; $p = .004$)	5.91 vs 6.24 (HR 0.82; 95% CI 0.69–0.99; $p = .038$)
Cunningham et al: J Clin Oncol 27:5513, 2009	Gemcitabine vs gemcitabine + capecitabine (GEM-CAP)	533	3.8 vs 5.3 (HR 0.78; 95% CI 0.66–0.93; $p = .004$)	6.2 vs 7.1 (HR 0.86; 95% CI 0.72–1.02; $p = .08$)
Von Hoff et al: N Engl J Med 369:1691, 2013	Gemcitabine vs gemcitabine + nab-paclitaxel	861	3.7 vs 5.5 (HR 0.69; 95% CI 0.58–0.82; $p < .001$)	6.7 vs 8.5 (HR 0.72; 95% CI 0.62–0.83; $p < .001$)
Conroy et al: N Engl J Med 364:1817, 2011	Gemcitabine vs FOLFIRINOX	342	3.3 vs 6.4 (HR 0.47; 95% CI 0.37–0.59; $p < .001$)	6.8 vs 11.1 (HR 0.57; 95% CI 0.45–0.73; $p < .001$)

Onkologie trial (CONKO 001) found that the use of gemcitabine after complete resection significantly delayed the development of recurrent disease compared with surgery alone. The European Study Group for Pancreatic Cancer 3 (ESPAC-3) trial, which investigated the benefit of adjuvant 5-fluorouracil/folinic acid (5-FU/FA) versus gemcitabine, revealed no survival difference between the two drugs. However, the toxicity profile of adjuvant gemcitabine was superior to 5-FU/FA by virtue of its lower incidence of stomatitis and diarrhea. Adjuvant radiotherapy is not commonly used in Europe based on the negative results of the ESPAC-1 study. Adjuvant 5-FU-based CRT with gemcitabine before and after radiotherapy as used in the Radiation Therapy Oncology Group (RTOG) 97-04 trial is preferred in the United States. This approach may be most beneficial in patients with bulky tumors involving the pancreatic head.

INOPERABLE LOCALLY ADVANCED DISEASE

Approximately 30% of patients present with locally advanced, unresectable, but nonmetastatic pancreatic carcinoma. The median survival with gemcitabine is 9 months. Patients who respond to chemotherapy or who achieve stable disease after 3–6 months of gemcitabine have frequently been offered consolidation radiotherapy. However, a large, phase III, randomized controlled trial, LAP-07, did not demonstrate any improvement in survival for patients treated with CRT after 4 months of disease control on either gemcitabine or a gemcitabine/erlotinib combination.

METASTATIC DISEASE

Approximately 60% of patients with pancreatic cancer present with metastatic disease. Patients with poor performance status do not usually benefit from chemotherapy. Gemcitabine was the standard treatment with a median survival of 6 months and a 1-year survival rate of only 20%. The addition of nab-paclitaxel (an albumin bound nanoparticle formulation of paclitaxel) to gemcitabine results in significantly improved 1-year survival compared to gemcitabine alone (35% vs 22%, $p < .001$). Capecitabine, an oral fluoropyrimidine, has also been combined with gemcitabine (GEM-CAP) in a phase III trial that showed an improvement in response rate and progression-free survival over single-agent gemcitabine, but no overall survival benefit. However, pooling of two other randomized controlled trials with this trial in a meta-analysis resulted in a survival advantage with GEM-CAP. Addition of erlotinib, a small-molecule epidermal growth factor receptor inhibitor, produced a statistically significant but clinically marginal benefit when added to gemcitabine in the advanced disease setting. A phase III trial limited to good performance status patients with metastatic pancreatic cancer showed improved survival with the combination of 5-FU/FA, irinotecan, and oxaliplatin (FOLFIRINOX) compared with gemcitabine, but with increased toxicity **(Table 112-2)**.

FUTURE DIRECTIONS

The early detection and future treatment of pancreatic cancer relies on an improved understanding of molecular pathways involved in the development of this disease. This will ultimately lead to the discovery of novel agents and the identification of patient groups who are likely to benefit most from targeted therapy.

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113 Endocrine Tumors of the Gastrointestinal Tract and Pancreas

Robert T. Jensen

GENERAL FEATURES OF GASTROINTESTINAL NEUROENDOCRINE TUMORS

Gastrointestinal (GI) neuroendocrine tumors (NETs) are tumors derived from the diffuse neuroendocrine system of the GI tract; that system is composed of amine- and acid-producing cells with different hormonal profiles, depending on the site of origin. The tumors historically are divided into GI-NETs (in the GI tract) (also frequently called *carcinoid tumors*) and pancreatic neuroendocrine tumors (pNETs), although newer pathologic classifications have proposed that they all be classified as GI-NETs. The term *GI-NET* has been proposed to replace the term *carcinoid*; however, the term *carcinoid* is widely used, and many are not familiar with this change. Accordingly, this chapter will use the term *GI-NETs* (carcinoids). These tumors originally were classified as APUDomas (for *a*mine *p*recursor *u*ptake and *d*ecarboxylation), as were pheochromocytomas, melanomas, and medullary thyroid carcinomas, because they share certain cytochemical features as well as various pathologic, biologic, and molecular features **(Table 113-1)**. It was originally proposed that APUDomas had a similar embryonic origin from neural crest cells, but it is now known the peptide-secreting cells are not of neuroectodermal origin. Nevertheless, the concept of APUDomas is useful because these tumors have important similarities as well as some differences (Table 113-1). In this section, the areas of similarity between pNETs and GI-NETs (carcinoids) will be discussed together, and areas in which there are important differences will be discussed separately.

CLASSIFICATION/PATHOLOGY/TUMOR BIOLOGY OF NETs

NETs generally are composed of monotonous sheets of small round cells with uniform nuclei, and mitoses are uncommon. They can be identified tentatively on routine histology; however, these tumors are now recognized principally by their histologic staining patterns due to shared cellular proteins. Historically, silver staining was used, and