Management of the Primary Tumor and Limited Metastases in Patients With Metastatic Pancreatic Cancer

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Abstract

New combinations of cytotoxic chemotherapy have been proven to increase response rates and survival times compared with single-agent gemcitabine for patients with metastatic pancreatic cancer. These responses have been dramatic for a subset of patients, therefore raising questions about the management of limited metastatic disease with surgery or other ablative methods. Similarly, for patients having a complete radiographic response to chemotherapy in the metastatic compartment, whether to consider local therapy in the form of radiation or surgery for the primary tumor is now an appropriate question. Therefore, collaboration among experts in surgery, medical oncology, and radiation oncology has led to the development of guiding principles for local therapies to the primary intact pancreatic tumor for patients with limited metastatic disease and those who have had a significant response after systemic therapy. (*J Natl Compr Canc Netw* 2015;13:e29–e36)

Pancreatic cancer (PCA) is one of the most challenging malignancies faced by patients, their families, and their physicians. Symptoms related to metastatic disease (eg, malaise, fatigue, cachexia, and venous thromboembolism) may all contribute to poor quality of life. Moreover, the local component of PCA may also be associated with significant morbidity, including pain, biliary obstruction,

gastrointestinal dysfunction or bleeding, and exocrine or endocrine pancreatic insufficiency. Fortunately, multidisciplinary engagement and multiple therapeutic modalities have gradually improved and been refined to optimize survival while preserving quality of life.

Currently, a convergence of several improved techniques and technologies, coupled with a better understanding of underlying tumor biology, now enables physicians to consider more aggressive therapies for select patients who present with limited metastatic disease.

First, improvements in cross-sectional imaging have facilitated the detection of very low-volume metastatic disease. Such metastatic foci, which can be limited to 1 or 2 lesions in a single organ, may have gone undetected in previous years. In addition, laparoscopy seems to be particularly effective in identifying occult metastatic disease that may otherwise be undetected by modern imaging modalities.^{1,2}

Second, a broader array of radiation options that include image-guided (IGRT) and stereotactic body radiation therapy (SBRT) have demonstrated encouraging efficacy in the treatment of primary and metastatic tumors while minimizing toxicity. Importantly, these techniques can be delivered over relatively short time courses, thus limiting the delay of systemic therapies. However, longer follow-up is needed to determine the full extent of late toxicity.

Third, recent advances in combination chemotherapy yield higher response rates and survival. Although uncommon, some isolated case reports of complete or near-complete radiographic responses have been observed after combination chemotherapy regimens. With the widespread adoption of novel combination chemotherapy regimens, larger subsets of

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patients with metastatic disease may be considered for novel clinical trials to manage the metastatic compartment as a way to preserve or improve quality of life.

Fourth, image-guided percutaneous radiofrequency ablation (RFA) and laparoscopically assisted RFA may allow for management of limited metastatic disease and spare patients the toxicity associated with ongoing cytotoxic chemotherapy.

Lastly, the morbidity and mortality associated with metastatectomies or primary PCA resections continues to decline, particularly in high-volume centers. Whether these interventions lead to improved overall survival (OS) or disease-free survival (DFS) in the setting of limited metastases is not yet known.

Role of Chemotherapy in Metastatic PCA

In 1996, weekly doses of gemcitabine proved to be modestly superior to weekly bolus fluorouracil. Furthermore, clinical benefit, an end point not commonly used in subsequent trials, was improved using gemcitabine compared with fluorouracil.³

Unfortunately, during the subsequent 15 years, although cytotoxic gemcitabine doublets often led to slightly higher objective response rates, no clinically or statistically significant survival benefit was observed in large randomized trials in which gemcitabine alone was compared with various gemcitabine doublets (cisplatin, oxaliplatin, irinotecan, fluorouracil, and capecitabine). The FDA approved the addition of erlotinib to gemcitabine, but the benefit was a mere few-week improvement in median OS. Moreover, the combination of gemcitabine with a variety of molecular agents—specifically bevacizumab, cetuximab, tipifarnib, and axitinib—demonstrated no improvement in objective responses or survival.⁴

In 2011, European investigators demonstrated that a combination of folinic acid, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) led to significantly higher response rates and survival times compared with gemcitabine (response rate, 32% vs 9%; median OS, 11.1 vs 6.8 months, respectively) in a group of patients with metastatic PCA.⁵ More recently, the combination of gemcitabine and nab-paclitaxel has likewise proven to be superior to gemcitabine alone for patients with metastatic PCA.⁶ Of

interest, the experimental arm generated complete radiographic responses in both trials, an observation not seen in patients treated with gemcitabine alone. However, dramatic tumor responses are not limited to FOLFIRINOX or gemcitabine plus nab-paclitaxel, and clinically significant anticancer activity has been reported for combinations of gemcitabine, docetaxel, and capecitabine (GTX).⁷

Although progress in the treatment of PCA has been incremental and uneven, as the scientific revolution in genomics, proteomics, and metabolomics converges with a greater understanding of host response and tumor microenvironment, more rapid advances in systemic therapy for PCA are certain to emerge. This may eventually lead to curative systemic therapies for patients with advanced disease. In the near-term, however, given the improved response rates currently being seen in clinical trials and practice, integration of other anticancer modalities can now be contemplated in select patients with a limited metastatic burden of disease.

Role of Surgical Management in Metastatic PCA

A small number of studies have identified that surgery can have a statistically significant survival advantage in selected patients with minimal metastatic disease.⁸ However, because the survival difference is so small, the clinical benefit may be negligible when considering a 6- to 8-week postoperative recovery time and a 35% to 45% operative morbidity. Thus, surgery in the presence of metastatic disease has been discouraged.

Conversely, the present rationale for proposing resection of the primary tumor in patients with metastatic PCA has been fueled by subset analyses that reveal significant improvements in survival of more than 4 months in patients who received both chemotherapy and surgery.^{9,10} A similar survival effect (3 months) was seen in patients who underwent palliative pancreaticoduodenectomy with gross residual disease.^{11,12} These findings, in addition to more effective multimodality therapies, suggest that a select group of patients with low-volume metastatic disease and good performance status may benefit from resection of the primary tumor if they also receive aggressive chemotherapy. However, other studies have shown no survival benefit when patients with meta-

static disease undergo aggressive surgical resection of the primary tumor and metastases.¹³ Therefore, additional clinical trials are warranted before these recommendations may be applied to the general population, because the subset of healthier patients selected for resection reflects potential selection bias.

Advances in radiologic and molecular diagnostic techniques have improved the ability to detect signs of minimal metastatic disease in patients with early-stage PCA. If all surgical candidates are assumed to have microscopic metastatic disease, how is it possible to properly select which patients should undergo upfront surgery versus systemic chemotherapy? Or should all surgical patients receive some form of neoadjuvant therapy? The following sections discuss these issues, as potential prognostic and predictive biomarkers in PCA are explained.

Management of Positive Peritoneal Cytology

The AJCC and NCCN consider positive peritoneal cytology (PPC) as M1, metastatic disease.¹⁴ PPC is often associated with advanced-stage disease and has therefore been correlated with a poor prognosis and considered a contraindication to resection.^{15,16} However, many of these earlier studies did not have a large population of resected patients with PPC. Therefore, a fair amount of controversy remains regarding PPC in patients with potentially resectable PCA with no other evidence of distant metastasis. Recently, several large patient series examining the clinical implication of PPC in resectable PCA revealed no difference in OS after resection.^{17–19} These patients with PPC had no 5-year survivors, were more likely to have recurrence in the peritoneum, and had a shorter DFS, but this did not reach statistical significance. Until more prospective data are available, only patients having had initial chemotherapy and conversion to negative washings should be considered for resection of the primary tumor.

Implications of Lymph Node Location at the Time of Surgical Resection

Surgeons who identify regional lymph node involvement at the time of surgery should proceed with curative surgical resection. Conversely, patients with nonregional lymph node metastases at the time of surgery are considered to have metastatic disease and are, therefore, not considered ideal candidates for curative surgical resection. Regional lymph nodes for cancers in the head of the pancreas are defined in

the AJCC 7th Edition to be “nodes along the common bile duct, common hepatic artery (CHA), portal vein, posterior and anterior pancreaticoduodenal arcades, and along the superior mesenteric vein and right lateral wall of the superior mesenteric artery (SMA),”²⁰ whereas the College of American Pathologists defines celiac nodes as regional lymph nodes for cancers involving the head of the pancreas.²¹ Regional nodes for tumors in the body or tail of the pancreas are “along the CHA, celiac axis, splenic artery, and splenic hilum.”²⁰ Therefore, this implies that aortocaval and left-sided SMA nodes are considered metastatic disease for all patients with PCA.

Data supporting these definitions are sparse. However, some literature suggests that certain lymph node basins have a poorer prognosis. For example, patients with positive CHA regional nodes have been reported as having inferior prognoses, with no patients surviving more than 4 years from resection.^{20,22,23} Patients with positive aortocaval lymph nodes have superior survival compared with those with CHA nodes; nonetheless, long-term survival is rare.^{24,25} Therefore, the authors suggest that the CHA and retropancreatic aortocaval nodal basins be sampled at the time of surgery. Rather than aborting surgery in these patients, it may be reasonable to incorporate a more aggressive adjuvant regimen and/or tailor adjuvant radiation therapy fields to encompass these nodal areas. Given the worse prognosis in this group of patients, future adjuvant therapy trials should consider stratifying patients based on “nonregional” versus “regional” lymph node metastases. Although positive lymph node metastases are a negative prognostic indicator, they do not preclude cure or long-term survival and should therefore not be considered a contraindication to an aggressive surgical approach.

Management of the Primary Tumor When Metastases Are Identified at Surgery

Previously published reports of pancreatic resection with simultaneous hepatic resections in the management of metastatic PCA reveal no survival advantage over chemotherapy alone.^{13,26,27} This suggests that an aggressive resectional approach to incidentally identify metastatic disease offers no survival advantage and could limit the ability to deliver systemic therapy postoperatively. If metastases are found during laparoscopic exploration, no further surgery is advised unless there is a known duodenal

obstruction, wherein consideration should be given to a duodenal bypass (gastrojejunostomy) and cholecystectomy, because covered and uncovered biliary stents can occlude the cystic duct and lead to cholecystitis. If survival is deemed short, an endoscopically placed stent is superior.²⁸ If metastases are discovered at open celiotomy, then prophylactic duodenal bypass and cholecystectomy with biliary bypass should be considered, because 20% of patients will eventually develop duodenal obstruction.²⁹ It is fairly well established that an intentional R2 resection should not be attempted.³⁰ No data exist regarding the performance of a prophylactic gastrojejunostomy at first operation versus a postoperative duodenal stent placement at the time of a later duodenal obstruction. However, a meta-analysis of duodenal stents versus gastrojejunostomy found that the latter was preferable for patients with a longer (>3 months) expectation of survival.³¹ Most clinicians would perform nonoperative bypass procedures and reserve surgery for patients for whom endoscopic attempts failed and were candidates for chemotherapy. Intraoperative celiac plexus block might be considered if the surgeon is comfortable with the technique.¹¹

Management of Metachronous Metastatic Disease

Most patients who undergo resection for cure will ultimately experience recurrence and die of metastatic disease. Characteristic metastatic sites are the peritoneum, liver, and lung. The value of metastasectomy has been supported in other gastrointestinal tumors and may improve outcomes in a highly selected group of patients with PCA who experience recurrence in the lung. Although not clearly understood, PCA that has a propensity to metastasize to the lung seems to have a different natural history. Investigation into the merits of pulmonary metastasectomy reveals that, in a highly selected group of patients with good performance status and with a long interval between primary resection and recurrence, pulmonary metastasectomy resulted in an improved median OS.³² The benefits of metastasectomy for metachronous liver lesions are far less clear. Although small studies have reported improved survival benefits from resection of metachronous liver lesions,³³ this practice should probably be discouraged until further investigation warrants its efficacy.

Management of the Primary Tumor in Patients With a Radiologic Complete Response of Metastatic Disease Following Chemotherapy

With improved combination chemotherapy regimens, more radiologic complete responses in patients with known metastatic disease have been seen. Pathologic complete response to neoadjuvant therapy in resectable PCA is associated with a better prognosis.³⁴ This suggests that treating patients with neoadjuvant chemotherapy with or without local therapy, such as radiation, may be important in predicting which patients are likely to benefit from resection of the primary pancreatic tumor in the future.

Role of Radiation Therapy, Embolization, and Ablation in Metastatic PCA

Although most patients with PCA die of metastatic disease, select patients may die of local progression or have primary tumors with a low burden of metastatic disease. In an autopsy study, Iacobuzio-Dona-hue et al³⁵ found that 30% of patients died of localized PCA only and that these patients were more likely to have intact SMAD4/DPC4 staining seen on immunohistochemistry of their tumor. Conversely, patients with SMAD4/DPC4-mutated status were more likely to die of widespread metastatic disease. Subsequent retrospective and prospective reports have shown conflicting results regarding SMAD4 status.^{36–38} Nevertheless, knowing SMAD4/DPC4 status may be helpful in determining which patients with metastatic disease may be good candidates for local radiation therapy.

Currently, in patients with metastatic PCA, standard chemoradiation is used only for local palliation or pending obstruction, because it can delay administration of full-dose chemotherapy. However, if a patient with PCA has oligometastatic disease that has been stable on chemotherapy for an extended period (eg, >6 months) or if a patient has local progression only, it may be reasonable to deliver chemoradiation during a planned break from chemotherapy.

An alternative method that may provide benefit in these patients is SBRT, a radiation technique that involves the delivery of focused radiation over 1 to 5 days to the pancreatic tumor or metastatic lesion with a small margin.³⁹ Historically, a single treatment with SBRT (25 Gy x 1 fraction) to the pancreas has been associated with high rates (>40%) of late grade 2 or

greater gastrointestinal toxicity.^{40,41} However, preliminary data from a recent multicenter phase II trial for locally advanced PCA demonstrated that more acceptable late gastrointestinal toxicity (<10%) may be achieved with fractionated SBRT (3–5 treatments over 1–2 weeks).⁴² Importantly, given the short course of therapy, SBRT may be more easily integrated with aggressive systemic chemotherapy regimens, such as FOLFIRINOX (infusional 5-FU, leucovorin, oxaliplatin, and irinotecan), gemcitabine plus nab-paclitaxel, or GTX (gemcitabine, docetaxel, and capecitabine). Furthermore, it is possible that SBRT could be used to treat locally advanced tumors in an attempt to prevent local progression, even in the setting of oligometastatic disease.

Although SBRT could be used in the treatment of metastatic pancreatic lesions, data are limited because these patients often develop multiple liver or lung metastases that are not amenable to focused SBRT. Moreover, historical systemic regimens are not able to prevent the subsequent spread of metastases. Nevertheless, multiple studies have established SBRT as an effective and well-tolerated treatment modality for colorectal liver metastases.^{43,44} With improved systemic therapies, SBRT may be more widely used to treat the primary tumor in select patients with a low burden of metastatic disease. SBRT can also be used to treat liver and lung metastases as long as there is an ample reserve of nonirradiated normal tissue.

In addition to SBRT, thermal ablation using microwave, cryoablation, or radiofrequency ablation (RFA) techniques has also shown promising results in treating limited metastatic PCA.^{45,46} Laparoscopic RFA, which has been suggested to be theoretically more precise than percutaneous RFA, appears to safely provide local control to hepatic tumors; in fact, a 16-year experience at the Cleveland Clinic recently reported on RFA as a technique to minimize morbidity and mortality.⁴⁷ A nonthermal ablation technique called *irreversible electroporation* can also be used for focal tumor ablation in small (<4 cm) locally recurrent/persistent and unresectable PCA. It has been suggested that this technique may limit damage to adjacent structures and blood vessels, although efficacy and toxicity data are lacking.^{48,49}

Intra-arterial radioembolization, although its role in metastatic PCA is unclear, has shown benefit in patients with liver metastases from breast, colon, and neuroendocrine tumors.^{50,51} Radioembolization

with yttrium-90 microspheres is feasible in patients with large-burden metastatic PCA,⁵² although limited data warrant additional clinical trials to determine its effect on clinical outcomes. After a Whipple resection or a biliary bypass, caution should be used when treating metastatic lesions with surgery, ablation, or radioembolization, because there may be a higher risk of liver abscess formation due to obligate colonization of the bile ducts from the biliary-enteric anastomosis.⁵³ This risk may be less with the use of SBRT, because this technique is noninvasive and the necrosis occurs more slowly when compared with ablation or transarterial chemoembolization. However, further investigation is necessary.

Future Directions and Conclusions

Biomarkers

Patient selection is one of the most important variables when considering therapy for advanced-stage disease, and predictive biomarkers are needed to improve patient stratification into the most appropriate treatment regimens. Biomarkers allow for individualized therapies to target specific mutations and molecular pathways that seem to be closely linked to pancreatic carcinogenesis, such as *KRAS*, *p16/CDKN2A*, *TP53*, *BRCA2*, *PALB2*, and *SPARC*.^{54,55} Despite the identification of promising molecular targets, no biomarkers except for carbohydrate antigen (CA 19-9) have been implemented for routine clinical use; levels greater than 200 U/mL are highly suggestive of metastatic disease. *SMAD4/DPC4* is another potential predictive marker for metastatic disease.³⁵ Predicting patterns of locoregional versus metastatic disease progression may allow physicians to accurately determine which patients may benefit from more aggressive local therapy. More of these types of predictive biomarkers will be available in the near future as information from large-scale sequencing projects identifies key genetic drivers.

Current Investigational Agents

Although FOLFIRINOX and gemcitabine/nab-paclitaxel have demonstrated clinically significant activity in metastatic PCA, improvements in response rates and survival are still needed. Investigation of novel agents for the treatment of PCA is underway. Whether any of these approaches will prove to be beneficial is uncertain. Nevertheless,

Figure 1 Treatment algorithm for patients who present with metastatic pancreatic cancer. Abbreviations: MMC, mitomycin C; RT, radiation therapy; SBRT, stereotactic body radiation therapy.

^aBased on performance status (see NCCN Guidelines for Pancreatic Adenocarcinoma¹⁴).

^bCui Y, Brosnan JA, Blackford AL, et al. Genetically defined subsets of human pancreatic cancer show unique in vitro chemosensitivity. Clin Cancer Res 2012;18:6519–6530.

^cIf bleeding, pain, or obstruction, consider palliative RT, surgery bypass, duodenal stent, and/or pain block.

^dDirected therapies include SBRT and ablation (limited data to support).

higher response rates with more durable complete responses will eventually lead to long-term survival in select patients with metastatic PCA. In the meantime, integration of the other modalities described earlier, when appropriately used, is likely to improve survival and quality of life, even when cure is not possible. Moreover, efforts to develop predictive biomarkers to better select cytotoxic agents, radiation therapy, molecular therapeutics, or immunotherapy will likely expand the proportion of patients being considered for local therapies directed against the

primary tumor or the metastatic compartment.

Principles for Management of Patients With Metastatic PCA

Based on review of the current literature, it is premature to speculate on the broad application of aggressive multimodality therapy for patients with metastatic disease. However, based on the current knowledge and clinical practice, it is beginning to be understood that for a handful of highly select patients, treatment of the metastatic site or primary tumor may offer meaningful clinical benefit. Some guiding principles to consider

when determining treatment of these select cases are as follows (Figure 1):

- Patients with good performance status and limited metastatic disease should be referred to a high-volume PCA center to:
 - ▶ Be considered for enrollment in a clinical trial, and
 - ▶ Undergo multidisciplinary review of other potential interventions beyond systemic therapy, intended to control limited metastatic disease and/or the primary tumor with careful attention to sequencing.
- Patients should be initially treated with a minimum of 4 to 6 months (based on tolerability and response) of systemic chemotherapy to identify who may benefit from aggressive local management or control of limited residual metastatic disease.
- If prolonged control of metastases is established with systemic therapy, select patients should be considered for minimally invasive interventions to address limited residual metastatic disease, particularly of the lung.
- Patients who achieve a complete response of metastatic disease after chemotherapy:
 - ▶ Should be considered for surgical resection of the primary only after a 2- to 3-month break from full-dose systemic therapy. If indicated, chemoradiation or SBRT to the primary could be considered during this period.
- In patients with known prior metastatic disease, laparoscopic staging with peritoneal washings should be performed and the patient should have negative cytology before a resection of the primary tumor or metastatic site is attempted.

Summary

New combinations of systemic therapy are sufficiently active to now consider more aggressive multimodal therapy for select patients with limited metastatic disease. Furthermore, surgical removal of the primary tumor or metastatic site may now be an appropriate strategy for a small subset of patients experiencing a complete radiographic response to systemic therapy. However, more studies are needed. Such interven-

tions are best performed after multidisciplinary review in high-volume centers with expertise in newer radiation techniques, minimally invasive surgery, and interventional radiology.

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