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PRACTICE GUIDELINE SERIES

Report from the 13th Annual Western Canadian Gastrointestinal Cancer Consensus Conference; Calgary, Alberta; September 8–10, 2011

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ABSTRACT

The 13th annual Western Canadian Gastrointestinal Cancer Consensus Conference was held in Calgary, Alberta, September 8–10, 2011. Health care professionals involved in the care of patients with gastrointestinal cancers participated in presentation and discussion sessions for the purposes of developing the recommendations presented here. This consensus statement addresses current issues in the management neuroendocrine tumours and locally advanced pancreatic cancer.

KEY WORDS

Neuroendocrine tumours, pancreatic cancer, systemic therapy, radiation

1. TERMS OF REFERENCE

1.1 Purpose

To develop the consensus opinion of oncologists and allied health professionals from across western Canada in an attempt to define best care practices and to improve care and outcomes for patients with gastrointestinal cancers.

1.2 Participants

Medical, radiation, and surgical oncologists and allied health professionals from western Canada involved in the care of patients with gastrointestinal malignancies.

1.3 Target audience

Health care professionals involved in the care of patients with gastrointestinal malignancies.

1.4 Basis of Recommendations

The recommendations reported here are based on presentation and discussion of the best available evidence (Table I). Where applicable, references are cited.

2. NEUROENDOCRINE TUMOURS

Question: What is the role of octreotide LAR (long-acting release) in the treatment of asymptomatic advanced low- and intermediate-grade midgut neuroendocrine tumours (NETS)?

- The PROMID study[2] showed a time-to-progression benefit for patients with metastatic low- and intermediate-grade midgut NETS (level I evidence).
- The data do not present a strong case for the immediate introduction of octreotide LAR therapy in those patients (level III evidence).
- Patients who become symptomatic, demonstrate disease progression, or have a biochemical indication for therapy could be considered for octreotide LAR therapy. Such patients should also be considered for multidisciplinary evaluation (level III evidence).

TABLE I Levels of evidence[1]

Level	*Meaning*
I	Evidence from one or more randomized controlled trials
II-1	Evidence from one or more controlled trials without randomization
II-2	Evidence from cohort or case–control analytic studies, preferably from more than one centre or research group
II-3	Evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments could be included here
III	Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees

Summary of Evidence: Neuroendocrine tumours are a group of rare neoplasms arising from neuroendocrine cells located throughout the body. The incidence of these tumours has increased significantly since the early 1970s[3]. More than 80% of NETs express a high density of somatostatin receptors, of which 5 subtypes have been identified[4].

The introduction of synthetic somatostatin analogs (SSAs) in the 1980s revolutionized the treatment of patients with functional NETs. These agents are effective in managing the symptoms associated with functional tumours in more than 50% of patients[5] and are used worldwide today for their palliative benefit. They are generally well tolerated.

A subject of controversy has been the treatment of nonfunctioning NETs with SSAs. *In vitro* studies suggest that SSAs may have an antiproliferative effect[6,7], but nonrandomized clinical studies have produced disappointing results, with tumour shrinkage according to World Health Organization or the Response Evaluation Criteria in Solid Tumors seen in fewer than 5% of patients. Stabilization of tumour growth is described in up to 50% of patients whose disease was progressing before treatment with SSAs[8].

The PROMID study is the first randomized prospective trial with data supporting the possible antineoplastic effect of octreotide LAR in a relatively homogeneous population of patients with midgut NETs. The primary endpoint of the study, time to progression, was significantly longer (15.6 months) in the experimental arm of the trial than in the control (placebo) arm (5.9 months)[2]. Patients benefitted equally, regardless of whether their tumour was functional or nonfunctional. The benefit of treatment as defined by the study on other important clinical outcomes such as overall survival (OS) is unknown.

Patients with advanced midgut NETs can be relatively asymptomatic from their disease, particularly with nonfunctional tumours. Patients may remain well or minimally symptomatic for months to years. The PROMID data do not present sufficiently strong evidence to suggest that all patients with advanced midgut NETs should be treated with octreotide LAR.

Patients with midgut NETs who become symptomatic, who have a biochemical indication for therapy, or who demonstrate disease progression should be considered for treatment with octreotide LAR based on the growing body of evidence that supports the use of that agent for the palliation of disease-related symptoms and for the potential antiproliferative benefits of treatment in the setting of progressive disease.

Question: What is the role of inhibitors of the mammalian target of rapamycin (MTOR) combined with octreotide in the treatment of advanced low- and intermediate-grade NETs?

- Treatment with everolimus and octreotide LAR may be considered in patients with a history of symptoms consistent with carcinoid and documented progressive disease (level I evidence)[9].
- Correcting for informative censoring bias, a 5.5-month progression-free survival (PFS) benefit was seen (level I evidence)[9].

Summary of Evidence: A serine/threonine kinase, MTOR plays a central role in cellular growth, proliferation, and metabolism and in angiogenesis[10–12]. Neuroendocrine tumours are linked to genetic alterations in inherited syndromes, including tuberous sclerosis, neurofibromatosis, and von Hippel–Lindau disease, in which upregulated MTOR inhibition is associated with the development of islet cell and carcinoid tumours[13–15]. Sporadic carcinoid tumours have been shown to co-express insulin-like growth factor 1 (IGF-1), an upstream activator of the MTOR pathway, and the IGF receptor[16]. Octreotide downregulates IGF-1 and reduces serum IGF-1 levels in patients with solid tumours[17], and everolimus inhibits MTOR[12], which suppresses the growth of NETs[16,18]. Combination therapy with octreotide and MTOR inhibitors is therefore a rational approach to the treatment of advanced NETs that has been investigated in clinical trials with interesting results.

In 60 patients with low- to intermediate-grade advanced NETs, Yao and colleagues demonstrated antitumour activity with the combination of octreotide LAR (30 mg every 28 days) with two dose schedules of everolimus (5 mg and 10 mg daily). This phase II study reported a response rate of 20% and disease stabilization in 70% of patients[19]. Combination therapy was associated with grade 3 and 4 toxicities in 10% of patients in the study.

The phase III RADIANT 2 study[20] randomized 429 patients with low- to intermediate-grade advanced NETs and carcinoid syndrome to octreotide LAR 30 mg every 28 days with either placebo or everolimus 10 mg daily. The heterogeneous study population included patients with small intestine, colon, lung, and other primary tumour sites. The primary outcome in this selected population of patients with documented radiographic progression of disease in the 12 months before commencement of therapy was PFS by central radiographic review. According to that review, PFS was prolonged by 5.1 months in patients treated with combination therapy. The trial failed to meet pre-specified statistical significance. Assessment of PFS by local investigators favoured the combination therapy arm with an improvement in PFS of 3.4 months, and a pre-specified statistical analysis of inverse probability of censoring weights supported a meaningful improvement in PFS. Treatment was associated with manageable toxicity and side effects consistent with those seen in other trials involving these agents.

In the phase III RADIANT 3 study, which was designed to assess the efficacy of everolimus in patients with advanced pancreatic NETs (PNETs), concomitant use of octreotide was permitted as part of best supportive care. Of patients treated on this trial, 40% received treatment with octreotide, providing additional evidence that the combination of octreotide and everolimus can be administered safely with a tolerable side effect and toxicity profile[9]. Ongoing trials, including the RADIANT 4 study, will help to further elucidate the potential benefits of combining SSA therapy and mTOR inhibition in selected patient populations with NETs other than PNETs.

At the present time, based on a sound preclinical rationale and data from phase II and III clinical trials, it is reasonable to consider treatment with a combination of everolimus and octreotide LAR in NET patients with a history of carcinoid symptoms and documented disease progression.

Question: What is the role of everolimus and sunitinib in the treatment of advanced pancreatic NETs?

- Both agents have demonstrated a PFS benefit compared with placebo in a randomized phase III trial setting. The magnitude of the benefit is similar for the two agents (level I evidence)[9,21].
- The optimal sequencing of these agents in reference to other treatment modalities has not been established (level III evidence).

Summary of Evidence: The study of PNETs and carcinoid tumours in patients with tuberous sclerosis and neurofibromatosis is in part responsible for the current understanding of the importance of the mTOR pathway in the pathogenesis of those malignancies[14,15]. The tuberous sclerosis complex (*TSC1/2*) and the neurofibromatosis (*NF1*) gene are regulators of the mTOR pathway in normal neuroendocrine cells[22–25].

Neuroendocrine tumours are highly vascular tumours[26] that overexpress vascular endothelial growth factor and its receptor. Autocrine activation of the vascular endothelial growth factor pathway may also potentiate tumour growth[27–29]. Signalling pathways that express platelet-derived growth factor and its receptor, IGF-1 and its receptor, and others have also been implicated in the pathogenesis of NETs[30–34].

Patients with PNETs often present with locally advanced (20%) or metastatic disease (60%)[9,35]. Median survival in patients with metastatic PNETs is 24–28 months[3,9,35], and 65% of patients with advanced disease will die within 5 years[35].

Systemic treatment with streptozocin-based doublets results in response rates of 10%–45%[36]. Treatment is inconvenient for patients, often necessitating travel to specialized facilities familiar with the administration of these agents and with their associated side effects and toxicities, which can be considerable. Not all patients with advanced PNETs are appropriate for treatment with streptozocin-based chemotherapy, and streptozocin is now available in Canada only through a special-access program. There remains a significant unmet need for effective, convenient, and tolerable systemic therapy for patients with advanced PNETs.

Based on the growing understanding of the potential role of mTOR and the vascular endothelial growth factor receptor in the pathogenesis of PNETs, clinical trials designed to test agents targeting those pathways have been completed or are ongoing worldwide. In February 2011, the published results of two randomized phase III trials in patients with advanced PNETs raised hope for patients living with those cancers. The trials were conducted in a selected population of patients whose disease had progressed in the 12 months before study entry.

In a trial involving 410 patients, Yao and colleagues[9] demonstrated a 6-month PFS improvement in patients treated with everolimus, an orally administered mTOR inhibitor, compared with patients receiving placebo. Treatment with everolimus was well tolerated, and the side effects and toxicities reported were consistent with those reported in clinical trials of that agent in other cancers.

Raymond and colleagues[21] reported the results of a phase III trial of orally administered sunitinib compared with placebo in patients with advanced PNETs. Because of a higher number of serious adverse events and deaths in the placebo arm of the study, the trial was discontinued after 171 of 340 patients had been accrued. The study demonstrated a clinically meaningful PFS prolongation of 6 months in patients treated with sunitinib.

Treatment with everolimus or sunitinib is appropriate for consideration in patients with advanced PNETs whose disease is progressing. At the present time, the selection of one agent over the other will likely be determined by the patient's comorbidities and the differing toxicity profiles of these drugs. The optimal sequencing of everolimus and sunitinib is not established and should be the subject of clinical trials.

Question: What is the role of resection of the primary tumour in the setting of advanced NETs?

- These patients should be referred to an experienced surgical team and reviewed in a multidisciplinary setting to define the most appropriate treatment options (level III evidence).
- Resection of the primary tumour may provide clinical benefit (level II-2 evidence).

Summary of Evidence: Patients having small-bowel NETs frequently present with metastatic mesenteric and liver disease. The primary is usually small and undetectable with standard imaging modalities. In the past, asymptomatic patients with advanced disease

were not referred for surgical resection. However, many centres of excellence in NETs have developed an aggressive surgical approach for these patients. Retrospective data have demonstrated improved survival in patients undergoing resection of the mesenteric disease compared with patients that did not (median survival: 11 years vs. 2.6 years)[37–39]. The suggestion is that resection of regional disease delayed onset of the obstruction and ischemia frequently seen in later stages of the disease. Although these data are biased because of surgical selection, it does appear that aggressive surgical resection of regional disease may improve palliation in these patients, who are often experiencing ischemic symptoms[38,40].

Furthermore, some investigators have retrospectively shown an improved median PFS of 56 months compared with 25 months in patients whose primary tumour was resected in the face of advanced liver disease[41]. The authors postulated that the primary tumour may be producing growth factors or peptides that promote the growth of the liver metastases. An ongoing prospective study is now looking at that very question. Further evidence to support the theory that the primary may play a significant role in survival was found in a recent multivariate analysis of 360 small-bowel NETs in the United Kingdom. Resection of the primary, age, and Ki67 index proved to be independent predictors of survival[42].

The ability to accurately predict the extent of disease both regionally and distantly on convention anatomic and functional imaging has been shown to be limited[43]. Imaging underestimated the disease found at laparotomy in 35% of the cases and failed to detect liver metastases in 15% of patients with clinical carcinoid syndrome. Surgical exploration by an experienced surgical team is the most accurate way to stage these patients. Thus, all patients with small-bowel NETs should be assessed early in the course of their disease within a multidisciplinary clinic where the appropriate surgical expertise is available[44].

Question: What is the role of debulking surgery in the management of advanced NETs?

- Debulking, performed by a specialized surgical team, should be considered in a multidisciplinary setting for patients with metastatic disease. Resection may offer benefits in terms of palliation, reduction of serum serotonin metabolite levels, outcomes, and response to subsequent therapies (level II-2 evidence).

Summary of Evidence: The management of metastatic NETs is largely a discussion concerning the therapy of metastatic lesions in the liver. Previous publications examining this topic gave the impression that a complete or R0 resection of metastatic disease was possible (similar to surgical resection of metastatic colorectal cancer). Recent work in this area has demonstrated that the disease pattern in these patients almost always involves multiple bilateral tumour deposits, often in a miliary pattern[38,45,46]. Consequently, it is almost always impossible to achieve an R0 resection. That having been said, strong evidence appears to demonstrate that aggressive maximal debulking of the hepatic disease is beneficial. Potential mechanisms of benefit include improved survival related to near complete extirpation of tumour, improved symptom control related to decreased endocrinopathy, less damage to the heart as a result of decreased systemic hormone levels, and facilitation of the delivery of other adjuvant therapies (radiolabelled and yttrium therapies). The goals of therapy therefore aim at improving survival or quality of life, or both. To accomplish those goals, surgical therapy needs to be delivered by a team with experience in both hepatobiliary and endocrine surgery. The treatment decisions should be made in the context of a multidisciplinary team and the need to include a full complement of therapies and adjuncts to surgical therapy so that residual disease not removed by surgery can be treated. The other therapies include (but are not limited to) systemic therapies; regional therapies, including radiolabelled and yttrium interventions; bland and chemoembolization; and ablative techniques. All patients should be assessed and considered for disease debulking. Surgical resection and debulking need to be done with low perioperative morbidity and mortality to be justified in the context of palliative surgery.

Question: What are the indications for radioisotope therapy in the management of NETs?

- Baseline octreotide and metaiodobenzylguanidine scans are required if radioisotope therapy is being considered (level III evidence).
- Indications for therapy include progressive disease or progressive symptoms, regardless of whether tumours are functional or nonfunctional (level III evidence).
- Prospective multicentre trials are required to better elucidate the indications for radioisotope therapy in this patient group (level III evidence).

3. LOCALLY ADVANCED PANCREATIC CANCER

Question: What is the definition of borderline resectable pancreatic cancer?

- To determine resectability status, these patients should be referred to an experienced surgeon with expertise in the surgical management of pancreatic cancers.
- We are in agreement with the consensus definition of borderline resectable pancreatic cancer

sponsored by the American Hepato-Pancreato-Biliary Association, the Society of Surgical Oncology, and the Society for Surgery of the Alimentary Tract[47], which includes these features:

- No distant metastases
- Venous involvement of the superior mesenteric (SMV) or portal vein demonstrating tumour abutment with or without impingement and narrowing of the lumen, encasement of the SMV or portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumour thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction
- Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis
- Tumour abutment of the superior mesenteric artery not to exceed 180 degrees of the circumference of the vessel wall

Summary of Evidence: The safety of surgical resection of pancreatic tumours has greatly improved in recent decades. In the 1970s, some authors suggested that it should be abandoned because of prohibitively high morbidity and mortality[48]. In recent years, pancreatic surgery has been associated with mortality approaching 1% in high-volume centres[49]. The improved safety profile of pancreatic surgery has led to more aggressive and complicated resections being undertaken. Consequently, the definition of what is technically resectable has also evolved. Large series of pancreaticoduodenectomies with venous resection have demonstrated low mortality and long-term survival equivalent to those without vascular resection[50]. Resection of the portal vein or SMV is now widely accepted. Resection and reconstruction of the celiac axis or superior mesenteric artery during pancreatic resection for adenocarcinoma remains much more controversial[51].

The definition of resectable disease varies, which creates difficulties in comparing results across studies and selecting appropriate surgical, neoadjuvant, and adjuvant therapies. To address those problems, considerable effort has been made to standardize the definition of resectable pancreatic cancer[47]. The concept of a category of "borderline resectable" pancreatic cancer has recently been advocated[52,53]. A consensus conference on the topic was recently jointly organized by the American Hepato-Pancreato-Biliary Association, the Society of Surgical Oncology, and the Society for Surgery of the Alimentary Tract[47]. From that conference[54], localized and resectable pancreatic cancer was defined as no distant metastases; no radiographic evidence of SMV and portal vein abutment, distortion, tumour thrombus, or venous encasement; and clear fat planes around the celiac axis, hepatic artery, and superior mesenteric artery. Tumours considered borderline resectable were also defined as noted earlier.

This distinction from resectable pancreatic cancer is important, because these patients are at higher risk of complications from the increased complexity of the surgery, at high risk of margin positivity, and at high risk of early systemic failure because of the advanced nature of the tumour. Consideration should there be given to neoadjuvant therapy for borderline resectable tumours[55]. Other authors have shown that a neoadjuvant approach may improve patient selection and lead to low rates of margin positivity and high survival rates despite the high-risk nature of the tumours[52].

Although ongoing study is likely to lead to further modification and refinement, the establishment of these standard definitions is an important step in the development of future studies of the treatment of pancreatic cancer. Standardizing these definitions based on objective radiologic features will improve the ability to make comparisons across future studies and represents an important advance in the research into treating pancreatic cancer.

Question: What is the role of systemic therapy in the management of locally advanced pancreatic cancer?

- In the absence of a clinical trial, patients with a good performance status can be considered for gemcitabine with or without erlotinib (level I evidence)[56,57].
- We encourage further investigation of FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, oxaliplatin) in this patient population

Summary of Evidence: Historically, patients with locally advanced pancreatic cancer (LAPC) have been included in trials with patients having metastatic disease, and thus the bulk of the chemotherapy knowledge for LAPC comes from trials that combined locally advanced and metastatic patients. Gemcitabine has been the standard treatment since the landmark trial by Burris and colleagues[56] that demonstrated an improvement in OS and clinical benefit (a composite measurement of performance status, analgesic use, and pain) with the use of gemcitabine compared with fluorouracil. Since then, numerous trials have attempted to assess the efficacy of various chemotherapy combinations compared with gemcitabine[58–65]. No individual phase III trial has demonstrated improved survival for combination chemotherapy compared with gemcitabine alone, although a mild improvement in survival was noted in a combined analysis of results from several trials with the combination of gemcitabine and a platinum agent[66] and with the combination of gemcitabine and capecitabine[63].

More recently, there has been significant interest in assessing the efficacy of molecularly targeted therapies given in combination with gemcitabine. A study by Moore and colleagues[57] demonstrated a statistically significant improvement in OS from the combination of gemcitabine and erlotinib (an epidermal growth factor receptor tyrosine kinase inhibitor) compared with gemcitabine alone. That clinical trial was, at the time, the only one to demonstrate an improvement in OS with combination therapy versus gemcitabine alone. The improvement in OS was statistically significant, but only in the range of several weeks, and therefore its clinical significance has been questioned. Despite the questions, combination therapy was adopted as the new standard of care in some centres. Numerous other studies assessing the efficacy of biologic agents, given either in combination with chemotherapy or alone, have been performed, but none has been able to demonstrate an improvement in OS compared with gemcitabine alone[67–70]. At the American Society of Clinical Oncology general meeting in 2010, the results of a phase III study comparing gemcitabine with FOLFIRINOX—a chemotherapy regimen combining fluorouracil, leucovorin, irinotecan, and oxaliplatin—were first presented[71]. The trial included only patients with good performance status, and it should be noted that a high percentage of patients had primary tumours in the body or tail of the pancreas, and were thus less likely than patients with head-of-the-pancreas tumours (the most common primary location seen clinically) to have biliary obstruction[72]. The trial results were impressive, with a response rate to FOLFIRINOX of 31.6% compared with 9.4% for gemcitabine and significant improvements in PFS (6.4 months vs. 3.3 months; hazard ratio: 0.47; $p < 0.001$) and OS (11.1 months vs. 6.8 months; hazard ratio: 0.57; $p < 0.001$) for FOLFIRINOX compared with gemcitabine. Given those results, FOLFIRINOX is now an option for first-line therapy in metastatic patients with good performance status. It should be noted that FOLFIRINOX was also associated with significant toxicity, including high rates of grade 3 or 4 neutropenia (45.7%).

The design of clinical trials in pancreatic cancer is evolving, and in keeping with recommendations from an expert consensus group[73], patients with LAPC are, for the most part, no longer included with metastatic patients in clinical trials of advanced pancreatic cancer. Patients with locally advanced disease were not included in the FOLFIRINOX trial, and therefore the results of that trial cannot be extrapolated to the LAPC population.

Data for the use of FOLFIRINOX in the LAPC population are limited. A small pilot study of neoadjuvant FOLFIRINOX in patients with LAPC was presented at the American Society of Clinical Oncology gastrointestinal cancer symposium in 2011[74]. A retrospective series of 12 patients with LAPC had been treated with neoadjuvant FOLFINOX. Of 10 evaluable patients, 6 were felt to have been converted to resectability, and 4 had R0 resections. The estimated median survival for that group was 20.7 months. These data are promising, but given the small size of the study, further research is needed.

At the current time, gemcitabine and the combination of gemcitabine and erlotinib remain the standard chemotherapy options for LAPC. The data on FOLFINOX in the metastatic setting are encouraging, but given that patients with LAPC were not included in the phase III trial and that only minimal data are available for that population, further investigation of the regimen in locally advanced disease is necessary. Several clinical trials investigating FOLFIRINOX either alone, in combination with a biologic agent, or given sequentially with chemoradiotherapy in the LAPC setting are planned or are currently ongoing (search for NCT01359007, NCT01413022, and NCT01397019 at http://Clinicaltrials.gov).

Chemoradiotherapy is another option for the treatment of LAPC[75], but controversy remains concerning whether it adds to chemotherapy alone and what the optimal timing and type of chemotherapy and radiotherapy are. More details are discussed in the evidence summary for the next question. An ongoing phase III study assessing whether the addition of chemoradiotherapy improves survival compared with systemic therapy alone will help to clarify the role of chemoradiotherapy in the management of LAPC[76].

Question: What is the role of combined chemoradiation in the management of LAPC?

- There is no consistent evidence of benefit with chemoradiation compared with chemotherapy in patients with LAPC (level III evidence).
- Chemoradiation could be considered in selected patients after discussion in a multidisciplinary setting (level III evidence).

Summary of Evidence: The addition of radiation to chemotherapy for LAPC continues to be a controversial issue. The support for radiation comes from older Radiation Therapy Oncology Group literature[77] as well as from the high local relapse rates reported in modern chemotherapy trials[78]. The rapid distant spread of pancreatic cancer and the lack of benefit from radiation in the European Study Group for Pancreatic Cancer and the European Organisation for Research and Treatment of Cancer 40891 trials (both of which examined chemoradiation only in the postoperative rather than the locally advanced setting) have adversely influenced the use of radiation for locally advanced tumours[79,80]. Furthermore, given the disappointing survival in LAPC, ongoing attempts to add increasing amounts of chemotherapy as opposed radiation continue to be pursued with very limited success[57,67].

With OS being closely correlated with distant disease spread, a pragmatic approach of beginning with 2–6 cycles of chemotherapy before delivering radiation is generally endorsed in current trials and by the conference[78,81,82]. That approach removes patients with early distant disease from the radiation-treated cohort, given that they would likely derive little benefit from radiation treatment. Theoretically, it also allows those who are at greater risk of local relapse (because of absence of disease spread) to receive further targeted local therapy to their site of greatest disease. Gemcitabine and fluorouracil–capecitabine both remain the standard chemoradiation agents, with many trials examining the role of other chemotherapeutics concurrent or sequential with chemoradiation.

Question: What is the role of stereotactic radiation in the management of LAPC?

- At present, no available evidence supports the use of stereotactic radiation in the management of LAPC.

Summary of Evidence: Stereotactic radiation has been demonstrated to be acutely well tolerated and convenient for patients. It allows for an increased radiation dose to be delivered to the pancreatic tumour in a reduced number of patient visits. It has also shown benefit in pain control. The increased local control of pancreatic cancer provided by stereotactic radiation has now been demonstrated by phase II trials from several institutions[83–87], but no head-to-head trials between stereotactic radiation and conventional three-dimensional conformal radiation have been conducted, and there is no evidence from randomized controlled trial of improved OS with stereotactic radiation. We recommend that stereotactic radiation continue to be studied in research settings sequential with chemotherapy.

4. ACKNOWLEDGMENTS

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5. CONFLICT OF INTEREST DISCLOSURES

DRu has acted in an advisory role for Novartis and Pfizer. The other authors have no financial conflicts of interest to declare.

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