Editorial

New possibilities and potential benefits for local control in locally recurrent pancreatic cancer

Shane Lloyd, Bryan W. Chang

Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, CT, USA

Corresponding to: Bryan W. Chang, MD. Yale University School of Medicine, 33 Cedar Street, P.O. Box 208040, New Haven, CT 06520-8040, USA. Email: bryan.chang@yale.edu.

Submitted Sep 13, 2013. Accepted for publication Sep 15, 2013.
doi: 10.3978/j.issn.2078-6891.2013.049
Scan to your mobile device or view this article at: http://www.thejgo.org/article/view/1553/2270

While pancreatic cancer remains an almost uniformly fatal diagnosis, data suggest that advances in treatment have resulted in modest gains in overall survival for local (1,2) and metastatic (2,3) disease. Possible explanations for these observations include earlier detection (lead-time bias) through improved imaging techniques, more accurate staging, and an increase in the rate of curative resections. However, survival benefits have been most convincingly demonstrated in the realm of improved systemic therapies. That is, the increased survival seen is certainly due in part to the success of gemcitabine-based (4) and FOLFIRINOX (5) chemotherapy in slowing the systemic spread of disease.

This is not to say that local control is irrelevant to survival. Local control has been shown to significantly impact survival in other cancer types when systemic disease is effectively controlled (6). However, the typical method used to report local control can hide its importance in diseases that commonly metastasize systemically. Patients are generally censored from the analysis at the time of death. Thus, favorable-appearing rates of local control can be misleading, and as survival improves, local control can appear to worsen as there is more time for locally advancing disease to become clinically apparent. When systemic control improves, local control becomes a more important metric in disease and symptom control (7).

In pancreatic cancer, local progression is likely the direct cause of death in a large proportion of patients. It has been shown that around 30% of patients with pancreatic cancer die with local progression alone (8-10) and 10-25% more experience local progression along with distant spread before death (9-11). Furthermore, because of close proximity to vital organ systems, local progression from pancreatic cancer is extremely morbid, and current treatment options are limited. For these reasons it is imperative to investigate methods to improve local control in this disease.

In this issue of the *Journal of Gastrointestinal Oncology*, Wild and colleagues report their experience with re-irradiation using stereotactic body radiation therapy (SBRT). Eighteen patients treated at two institutions were identified. Patients received re-irradiation with SBRT for isolated local recurrence after surgery and multimodality therapy (15 patients), or isolated local progression after definitive chemotherapy and radiation (3 patients). All patients received gemcitabine maintenance therapy and had no evidence of distant metastasis prior to re-irradiation with SBRT. The median re-irradiation dose was 25 Gy in 5 fractions. The authors report a median survival from the time of SBRT of 8.8 months (95% CI of 1.2-16.4 months). Effective symptom palliation occurred in 4 of 7 patients who reported abdominal or back pain prior to SBRT. Rates of toxicity were acceptable with only 5 cases (28%) of grade 2 acute toxicity, no cases of grade ≥3 acute toxicity, and only 1 case (6%) of grade 3 late toxicity.

These results are encouraging, but proper patient selection is essential. The authors report that those patients who experienced local progression 9 months or more after definitive therapy survived significantly longer (11.3 *vs.* 3.4 months; P=0.019) than those who progressed earlier. For those patients who progress early, this finding is further disappointing evidence of our very limited ability to control aggressive pancreatic cancer. It also lends support to the principle that local therapy is most beneficial for those patients who betray less aggressive disease, as seen in the multimodality treatment of localized-unresectable pancreatic cancer (12-14). Differences in tumor markers such as Smad4 (Dpc4) are being investigated (8,15) to help select appropriate patients for more intense local therapy. Finally, the authors appropriately excluded patients with poor performance status.

SBRT has many advantages in the setting of locally recurrent pancreatic cancer. Compared to fractionated

radiation therapy, SBRT shortens the treatment time, and may come with improved image guidance capabilities and dose conformality. Fears of high rates of late adverse effects from hypofractionation are not borne out in this study and seem to be less than 10-15% in other experiences of SBRT for pancreatic cancer in the recurrent (16), and definitive/adjuvant (17-19) settings. However, higher rates of toxicity have been seen with doses of 45 Gy in 3 fractions (20). Compared to surgery, SBRT offers the ability to resume chemotherapy faster, is less invasive, and avoids surgical morbidity. Finally, compared to chemotherapy alone or best supportive care, SBRT may theoretically improve freedom from further local progression and may even be cost effective if it can decrease the need for hospital admissions and interventional procedures to palliate pain and locally advancing disease.

In conclusion, local control is probably important for both symptom control and survival in pancreatic cancer but improving local control has been challenging. In the small retrospective series reported so far, re-irradiation with SBRT after local progression shows promise and adheres to the principle of "first, do no harm." For now, appropriate patients include those with a moderate time from definitive treatment to local-only progression and good performance status. Certainly, further investigation of re-irradiation with SBRT is warranted and the work of Wild and colleagues should inform future trials. We should move away from the nihilistic attitude that attempting to gain local control is not worthwhile and move towards a personalized approach to the treatment of pancreatic cancer.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Barugola G, Partelli S, Crippa S, et al. Time trends in the treatment and prognosis of resectable pancreatic cancer in a large tertiary referral centre. HPB (Oxford) 2013. [Epub ahead of print].
2. Riall TS, Nealon WH, Goodwin JS, et al. Pancreatic cancer in the general population: Improvements in survival over the last decade. J Gastrointest Surg 2006;10:1212-23; discussion 1223-4.
3. Worni M, Guller U, White RR, et al. Modest improvement in overall survival for patients with metastatic pancreatic cancer: a trend analysis using the surveillance, epidemiology, and end results registry from 1988 to 2008. Pancreas 2013;42:1157-63.
4. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15:2403-13.
5. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.
6. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366:2087-106.
7. Hellman S, Weichselbaum RR. Importance of local control in an era of systemic therapy. Nat Clin Pract Oncol 2005;2:60-1.
8. Iacobuzio-Donahue CA, Fu B, Yachida S, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. J Clin Oncol 2009;27:1806-13.
9. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350:1200-10.
10. Asiyanbola B, Gleisner A, Herman JM, et al. Determining pattern of recurrence following pancreaticoduodenectomy and adjuvant 5-flurouracil-based chemoradiation therapy: effect of number of metastatic lymph nodes and lymph node ratio. J Gastrointest Surg 2009;13:752-9.
11. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 2007;297:267-77.
12. Huguet F, André T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. J Clin Oncol 2007;25:326-31.
13. Krishnan S, Rana V, Janjan NA, et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. Cancer 2007;110:47-55.
14. Lloyd S, Chang BW. A comparison of three treatment strategies for locally advanced and borderline resectable pancreatic cancer. J Gastrointest Oncol 2013;4:123-30.
15. Crane CH, Varadhachary GR, Yordy JS, et al. Phase II trial of cetuximab, gemcitabine, and oxaliplatin followed by chemoradiation with cetuximab for locally advanced (T4) pancreatic adenocarcinoma: correlation of Smad4(Dpc4) immunostaining with pattern of disease progression. J Clin Oncol 2011;29:3037-43.
16. Lominska CE, Unger K, Nasr NM, et al. Stereotactic body radiation therapy for reirradiation of localized

adenocarcinoma of the pancreas. Radiat Oncol 2012;7:74.
17. Koong AC, Christofferson E, Le QT, et al. Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 2005;63:320-3.
18. Mahadevan A, Jain S, Goldstein M, et al. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 2010;78:735-42.
19. Rwigema JC, Parikh SD, Heron DE, et al. Stereotactic body radiotherapy in the treatment of advanced adenocarcinoma of the pancreas. Am J Clin Oncol 2011;34:63-9.
20. Hoyer M, Roed H, Sengelov L, et al. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. Radiother Oncol 2005;76:48-53.

Cite this article as: Lloyd S, Chang BW. New possibilities and potential benefits for local control in locally recurrent pancreatic cancer. J Gastrointest Oncol 2013;4(4):340-342. doi: 10.3978/j.issn.2078-6891.2013.049

