Ann Surg Oncol (2019) 26:4166–4167
https://doi.org/10.1245/s10434-019-07787-w

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – PANCREATIC TUMORS

Radiotherapy as an Adjunct to Surgery for Pancreatic Cancer: Where Are We After More Than 30 Years of Research and Trials?

Anthony Ferrantella, MD[1], Vikas Dudeja, MD[1], and Chandrakanth Are, MD, MBA[2]

[1]Department of Surgery, Division of Surgical Oncology, University of Miami, Miami, FL; [2]Department of Surgery, Division of Surgical Oncology, University of Nebraska Medical Center, Omaha, NE

Pancreatic cancer is an aggressive disease with poor outcomes. Currently, the only treatment that offers a chance for cure is surgical resection. However, decades of experience with surgical resection has demonstrated that this modality alone is associated with near universal, local recurrence, and/or metastases. Given the success of chemotherapy and radiotherapy in reducing recurrence in other diseases, this paradigm has been evaluated in pancreatic cancer as well, although with mixed success. While clinical trials have clearly shown an advantage of adjuvant chemotherapy, the data with respect to the use of radiation therapy to improve outcomes are mixed at best and negative at worst. The manuscript by Vela et al. in the current issue takes another look at this problem and evaluates the benefit of radiotherapy and its cost to society.[1] The authors used a population-based administrative dataset from a single-payer healthcare system in Ontario, Canada, to retrospectively evaluate the impact of chemoradiotherapy (CRT) on survival and its cost differential compared with chemotherapy. While this study, similar to other large population database studies, has many drawbacks in terms of selection bias and completeness of data, it reiterates the message that the use of CRT may be associated with unnecessary cost without overt benefit.

The justification for using CRT for pancreatic cancer stems from its theoretical benefit due to the high risk of local recurrence after resection, high rates of positive retroperitoneal margins and the adverse impact of this finding on survival. Supporters of this approach have long since cited the GITSG trial, which demonstrated a survival benefit with CRT compared with surgery alone after margin negative resection.[2] However, this very small phase III study (49 patients randomized to surgery + CRT vs. surgery alone) employed chemotherapy and radiation regimens that are far outdated in today's landscape of cancer therapies. Also, this trial did not attempt to separate the benefit of chemotherapy versus radiation therapy. Furthermore, these results either have not been reproduced or have been contradicted in subsequent trials, thus casting a cloud on the role of radiation therapy. For instance, the EORTC trial, which boasted a much larger number of patients, demonstrated a small but statistically insignificant improvement in survival for patients with pancreatic cancer who received adjuvant CRT.[3,4] On the other hand, the results of the ESPAC-1 trial, which with its complex design randomized patients by a 2×2 factorial design into observation versus chemotherapy or observation versus CRT, while having cleared the path for the use of adjuvant chemotherapy, created further controversy for the use of CRT, because CRT led to worse outcomes in this trial.[5] While this trial has led European centers essentially to minimize the use of adjuvant radiotherapy, adjuvant radiotherapy continues to be commonly used in North America. The proponents of CRT cite a lack of standardization as well as use of antiquated techniques and technology as the cause of failure of CRT to show efficacy in RCTs.

First Received: 16 August 2019;
Published Online: 11 October 2019

C. Are, MD, MBA
e-mail: care@unmc.edu

Similar to the RCTs evaluating the question of adjuvant CRT for pancreatic cancer, multiple, retrospective, single- and multi-institutional studies have supported the views on either side of the aisle.[6,7] In this regard, the study by Vela et al. takes another fresh look at this issue. They have employed linked administrative and pathological datasets to identify all patients diagnosed with pancreatic cancer in Ontario between 2004 and 2014. After stratifying by margin status and controlling for confounders, this analysis suggests that chemo-radiation does not offer any advantage over chemotherapy alone. Above and beyond the data reported by previous retrospective reviews, this study provides an additional perspective—that of the cost to society. According to their analysis, CRT is 25% more costly than chemotherapy, and this cost does not provide patients any advantage. In a world with ballooning healthcare costs, it is important to perform cost–benefit analyses, and it is difficult to justify an intervention that is costlier than its counterpart when it has not been proven to be beneficial beyond reasonable doubt.

Besides its use as adjuvant therapy, CRT has found its way into the neoadjuvant arena as well. Just like in the adjuvant setting, the theoretical benefits are many. Ensured delivery of therapy, conversion to resectable disease, and higher rates of margin negative resection are some of the proposed benefits. However, in this setting too, the addition of radiation has been performed without any clear supporting evidence, and it is unclear whether it is better or even equivalent to chemotherapy alone. In this regard, the negative findings from the LAP07 trial are clearly worrisome.[8] Before we get into another quagmire, i.e., widespread adoption before availability of clear evidence on the use of CRT as a neoadjuvant strategy, it is critical that well-thought clinical trials are conducted to evaluate the efficacy of this component of therapy for the treatment of pancreatic cancer, so that we not only avoid the unnecessary cost but also spare our patients unnecessary toxicity.

REFERENCES

1. Vela N, Davis LE, Cheng SY, et al. Economic analysis of adjuvant chemo-radiotherapy compared to chemotherapy in resected pancreas cancer. *Ann Surg Oncol*. 2019 [Epub ahead of print].
2. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg*. 1985;120:899–903.
3. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg*. 1999;230:776–82; discussion 782–4.
4. Smeenk HG, van Eijck CH, Hop WC, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. *Ann Surg*. 2007;246:734–40.
5. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet*. 2001;358:1576–85.
6. Hsu CC, Herman JM, Corsini MM, et al. Adjuvant chemoradiation for pancreatic adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. *Ann Surg Oncol*. 2010;17:981–90.
7. Merchant NB, Rymer J, Koehler EA, et al. Adjuvant chemoradiation therapy for pancreatic adenocarcinoma: who really benefits? *J Am Coll Surg*. 2009;208:829–38; discussion 838–41.
8. Hammel P, Huguet F, van Laethem JL, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 Randomized Clinical Trial. *JAMA*. 2016;315:1844–53.