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Review

Neoadjuvant Strategy as Initial Treatment in Resectable Pancreatic Cancer: Concrete Evidence of Benefit

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Abstract. *Pancreatoduodenectomy remains the recommended treatment in potentially curative strategies for pancreatic carcinoma. Due to high local failure rates even after complete resection, a multi-modality treatment approach is paramount in the management of resectable disease. Despite there being insufficient evidence to recommend a specific neoadjuvant strategy, several studies have tested the use of preoperative chemoradiotherapy in this sub-group of patients, achieving promising results. The treatment is well-tolerated, with higher rates of negative margins and lower rates of lymph node positivity at resection, a decrease in local failure and benefit in overall survival. Considering the poor oncological results after primary surgical treatment, neoadjuvant strategy should be considered as a valid alternative in resectable pancreatic carcinoma.*

Pancreatic cancer is the fourth cause of cancer-related death in both sexes (1). Surgical resection, radiation therapy, chemotherapy, or combined modality approaches represents the general management for patients with pancreatic cancer. The choice of treatment modality, whether singly or in combination, depends on the stage and size of the tumor and on factors related to patients, such as performance status, comorbidity, toxicity and convenience. A small number of patients (10%-20%) have a potentially resectable disease at diagnosis, but despite curative resection, the incidence of local failure ranges from 50% to 86% (2). Adjuvant therapy has been employed to minimize local failure risk, guaranteeing a modest (9 months) improvement in survival, and despite the well-supported role of chemotherapy, the role of radiation therapy continues to be controversial (3, 4).

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While there is general agreement on use of adjuvant treatment, there are differences concerning neoadjuvant strategies. The application of preoperative therapy to the treatment of pancreatic cancer dates back to the 1980s (5). Over the years, the role of radiation therapy, with or without chemotherapy, has advanced from initial use only in the surgically unresectable setting to testing of its use in the multimodality treatment management of resectable tumors (2). The advantage of radiation, with or without concurrent chemotherapy, has been further examined in the context of a meta-analysis (6). Although the trials included vary with respect to radiation dose, fractionation schedule, and chemotherapy regimen, conclusive data identify a small survival benefit for the use of neoadjuvant therapy, but do not suggest its clear role in evidence-based clinical practice. With neoadjuvant therapy, the median survival time is 23.3 months compared to 22.4 months after primary surgery followed by adjuvant therapy. Motivated by the need for supporting these significant results, the aim of this review was to elucidate the rationale for a neoadjuvant strategy in resectable pancreatic cancer and to provide an appropriate tool for better awareness of this issue.

Summary of Staging

Most pancreatic carcinomas (approximately 90%) are adenocarcinomas. Due to different natural history, other histological types are not considered in this review.

The definition of staging criteria for pancreatic cancer are based on the tumor/node/metastasis (TNM) system (7). However for clinical purposes, pancreatic cancer is usually staged as resectable, borderline-resectable and unresectable disease (Table I). Considering our purpose, we only introduce specific information to determine resectable status. Definition of resectable disease includes a tumor extending beyond the pancreas but without encasement of the celiac artery or the superior mesenteric artery, and an unobstructed portal vein and superior mesenteric vein.

The Background to Neoadjuvant Treatment

Since 1935, pancreatoduodenectomy remains the gold standard surgical treatment for resectable pancreatic cancer (8). The high risk of local recurrence after surgery is linked to the clinical anatomical relationships of the gland, as well as to the intrinsic invasive nature of pancreatic carcinoma. The pancreas is a retroperitoneal structure of the upper abdomen, strictly related to the mesenteric vessels. Even though significant improvement has been obtained in the characterization of primary stage disease, the tendency for lymphatic spread and hematogenous dissemination often culminate in non-radical resection, whether macro- or microscopic (9, 10). Unlike curative surgical resection of rectal, gastric and esophageal cancer, pancreato-duodenectomy necessitates complete biliodigestive reconstruction. This implies protracted postoperative hospitalization, hindering prompt adjuvant treatment. Literature data report a rate of 22% to 30% of patients who did not receive planned therapy (11-12). Consequently, the impact on survival may be significantly influenced by the slow accrual in trials testing appropriate adjuvant therapy (13,14). High local failure rates and the high risk of relapses due to delay of adjuvant treatment justify the interest in testing preoperative treatment as a new approach.

The Rationale for Neoadjuvant Treatment

In patients with potentially resectable pancreatic cancer, neoadjuvant therapy *i.e.* radiation therapy, with or without chemotherapy, given before surgery, aims to minimize local recurrence and to maximize survival. A down-staging effect, in this context, is not the main objective because the disease is considered surgically-resectable at the time of diagnosis.

There is a strong rationale for a neoadjuvant approach based on several fundamental assumptions. Notable advantages of preoperative radiation therapy include its effectiveness on well-vascularized tissue due to the oxygen effect. Moreover, preoperative radiation therapy potentially sterilizes the surgical field, with an increased probability of negative microscopic margins, especially retroperitoneally. Preoperative radiation treatment carries the advantage that all patients can receive neoadjuvant treatment, with an improved ability to tolerate it. Moreover, combined therapy is not associated with toxicity that delays surgery. On the contrary, considering distant metastases as a component of failure, preoperative therapy can potentially improve the control of micrometastatic disease and identifies rapidly progressive disease, reducing pancreatic resection for patients with no probability of cure.

Although preoperative radiotherapy can produce changes in tissues in the surgical bed, the choice of appropriate timing of surgery (not more than 45-60 days after the end of neoadjuvant therapy) can significantly reduce surgical problems, as demonstrated in neoadjuvant rectum radiotherapy (15).

Despite these theoretical considerations explaining the potentially favorable impact of neoadjuvant treatment on survival, whether radiation therapy should be delivered before or after pancreaticoduodenectomy remains unclear.

The Clinical Evidence Neoadjuvant Treatment

Promising results from several prospective trials (12, 16-18) and retrospective studies (19, 20) of preoperative chemoradiotherapy in localized and potentially resectable pancreatic cancer are available in the literature. The heterogeneity of data and a statistically underpowered analysis are the major factors restricting validation of the theoretical advantages of this strategy.

A role for preoperative multimodality therapy in resectable cancer is supported by some studies that combined radiation therapy with 5-fluoruracil-based chemotherapy. These single-Institute experiences confirmed excellent locoregional control, with a median overall survival of 15.7 to 25 months in patients treated with combined modality therapy (16-18).

Hoffmann *et al.* conducted a clinical trial of preoperative multimodality therapy (16). Out of 53 patients, 24 underwent tumor resection, with a median survival of 15.7 months *vs.* 9.7 months for the entire group. Pisters *et al.* reported overall survival of 25 months in patients who underwent neoadjuvant therapy compared with 7 months in those not submitted to surgery (17). Staley *et al.* evaluated survival in 39 patients treated by preoperative chemoradiation; it resulted in improved local control, with a median survival of 19 months (18).

Based on radiosensitizing properties of gemcitabine and on its efficacy in advanced pancreatic cancer (19, 20), a few trials investigated gemcitabine in association with radiation therapy as an alternative approach in the neoadjuvant setting. Talamonti *et al.* reported the results of a phase II trial testing preoperative gemcitabine and radiation therapy in 20 patients with resectable pancreatic carcinoma, which led to a median overall survival of 26 months (21).

There are no randomized data from randomized phase III trials comparing neoadjuvant treatment with adjuvant strategies. A recent multi-Institutional study provided a large retrospective database analysis comparing effects of neoadjuvant and adjuvant approach on patient survival. Colbert *et al.* reported data from 5,414 patients submitted to preoperative (277 patients) or postoperative (5,137 patients) chemoradiotherapy (22). This cohort study reported overall survival not to be inferior (18 months *vs.* 19 months), with higher rates of negative margins (82% *vs.* 72%), and lower rates of lymph node positivity at resection (41% *vs.* 65%) in patients receiving neoadjuvant therapy. Data from the study by Spitz *et al.* suggested no statistically significant difference in median survival (19.2 and 22 months, respectively) between pre- and postoperative chemoradiation strategies in 142 patients with localized pancreatic cancer (12). A

Table I. *Staging system for pancreatic cancer.*

TNM stage	Clinical stage	Criterion
T1-3 N0-1 M0	Resectable	Tumor extends beyond the pancreas but without encasement (<180˚ involvement) of CA or SMA and unobstructed PV and SMV.
T4 any N M0	Borderline resectable	Tumor abutment (≤180˚ or ≤50%) of CA or SMA circumference or >180˚ or >50% CHA that is amenable to resection and repair, or SMV or PV occlusion amenable to resection and interposition grafting.
Any T any N M1	Unresectable	Locally advanced (tumors that are involved with nearby structures to an extent that renders them unresectable) or metastatic disease.

CA: Celiac artery; SMA: superior mesenteric artery; PV: portal vein; SMV: superior mesenteric vein; CHA: common hepatic artery.

significant survival benefit for the use of neoadjuvant radiation therapy over adjuvant therapy (23 months vs.17 months) was reported by Stessin *et al*. (23), but due to limitations of SEER database analysis, definitive results must be validated. Again, a significantly better overall survival after neoadjuvant therapy compared with adjuvant treatment (33.8 *vs*. 19 months) was demonstrated by Artinyan *et al*. (24). Table II shows a review of the literature.

The Current Status of Neoadjuvant Treatment

Neoadjuvant treatment has been tested extensively in the management of gastrointestinal cancer (15, 26, 27). Despite a significant improvement on local control being detected in rectal (15, 25) and esophageal cancer (26), neoadjuvant radiation, with or without chemotherapy, still remains experimental for pancreatic cancer. At the current time, neoadjuvant chemoradiotherapy ensures similar resection frequencies and survival rates to those of adjuvant treatment (6). On the basis of data from trials, considering that patients submitted to preoperative chemoradiotherapy may have had initially more adverse prognostic features,assessing the real therapeutic value of neoadjuvant treatment is complicated. Better patient selection would probably increase the survival rate. Therefore, future trials should enroll homogeneous patient populations to clarify definitive conclusions. Randomized trials focusing on the impact of survival after neoadjuvant chemoradiotherapy are in progress (27-29). Open areas of investigation include advanced irradiation techniques – such as radiosurgery, proton beam therapy, intra-operatory radiotherapy) – and more effective combinations of drugs – such an oxaliplatin, irinotecan, 5-fluorouracil, bevacizumab, and nab-paclitaxel.

Conclusion

It is likely that the addition of radiotherapy with/without chemotherapy to surgical treatment for resectable pancreatic cancer would guarantee a survival benefit. Even though there are no solid data from randomized controlled trials, the benefit of preoperative therapy in these patients should not be underestimated.

Table II. *Summary results of neoadjuvant trials for survival in resectable pancreatic cancer.*

Study	Median survival (months)		
	Pre RT-CHT	Post RT-CHT	*p*-Value
Spitz *et al*. (12)	19.2	22.0	*
Colbert *et al*. (22)	18.0	19.0	0.077
Stessin *et al*. (23)	23.0	17.0	<0.01
Artinyan *et al*. (24)	33.8	19.0	0.003
Hoffmann *et al*. (16)	15.7	*	*
Pisters *et al*. (17)	25.0	*	*
Staley *et al*. (18)	19.0	*	*
Talamonti *et al*. (21)	26.0	*	*

Pre RT-CHT: Preoperative chemoradiotherapy; post RT-CHT: postoperative chemoradiotherapy; *not stated.

Conflicts of Interest

No conflicts of interest.

References

1 Siegel R, Ma J, Zou Z and Jemal A: Cancer statistics, 2014. CA Cancer J Clin *64*: 9-29, 2014.
2 Shah AA and Chao KSC: Pancreas and hepatobiliary tract. *In*: Chao KSC, Perez CA and Brady LW: Radiation Oncology Management Decicions. Third edition. Philadelphia, PA: Lippincott Williams & Wilkins, pp. 427-442, 2011
3 Abrams RA, Winter KA, Regine WF, Safran H, Hoffman JP, Lustig R, Konski AA, Benson AB, Macdonald JS, Rich TA and Willett CG: Failure to adhere to protocol specified radiation therapy guidelines was associated with decreased survival in RTOG 9704 – a phase III trial of adjuvant chemotherapy and chemoradiotherapy for patients with resected adenocarcinoma of the pancreas. Int J Radiat Oncol Biol Phys *82(2)*: 809-816, 2012.

4 Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, Beger H, Fernandez-Cruz L, Dervenis C, Lacaine F, Falconi M, Pederzoli P, Pap A, Spooner D, Kerr DJ, Büchler MW and European Study Group for Pancreatic Cancer: A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med *350(12)*: 1200-1210, 2004.
5 Pilepich MV and Miller HH: Preoperative irradiation in carcinoma of the pancreas. Cancer *46(9)*: 1945-1949, 1980.
6 Gillen S, Schuster T, Meyer Zum Büschenfelde C, Friess H and Kleeff J. Preoperative/ neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med *7(4)*: e1000267, 2010.
7 Edge S, Byrd D, Compton C, Fritz AG, Greene FL and Trotti A: Pancreas: *In*: Edge S, Byrd D, Compton C, Fritz AG, Greene FL and Trotti A: AJCC Cancer Staging Manual, Seventh Edition. New York, NY: Springer Verlag, pp. 155-163, 2009.
8 Whipple AO, Parsons WB and Mullins CR: Treatment of carcinoma of the ampulla of Vater. Ann Surg *102(4)*: 763-779, 1935.
9 Ridwelski K, Meyer F, Schmidt U and Lippert H: Results of surgical treatment in ampullary and pancreatic carcinoma and its prognostic parameters after R0-resection. Zentralbl Chir *130(4)*: 353-361, 2005 (in German).
10 Trede M, Schwall G and Saeger HD: Survival after pancreatoduodenectomy. 118 consecutive resections without an operative mortality. Ann Surg *211(4)*: 447-458, 1990.
11 Klinkenbijl JHG, Sahmoud T, van Pel R, Couvreur ML, Veenhof CHN, Amaud JP, Henrnprnan A, Wils J and Jeekel J: Radiotherapy and 5-FU after curative resection for the cancer of the pancreas and peri-ampullary region: A phase III trial of the EORTC GITCCG. Eur J Cancer *33(8)*: S274, 1997.
12 Spitz FR, Abbruzzese JL, Lee JE, Pisters PW, Lowy AM, Fenoglio CJ, Cleary KR, Janjan NA, Goswitz MS, Rich TA and Evans DB: Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. J Clin Oncol *15(3)*: 928-937, 1997.
13 Anon: Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Gastrointestinal Tumor Study Group. Cancer *59(12)*: 2006-10, 1987.
14 De Felice F, Musio D, Cassese R, Masi D and Tombolini V: Adjuvant therapy of pancreatic carcinoma: the experience of Policlinico Umberto I, Università "Sapienza" Rome. Gastrointestinal Cancer: Targets and Therapy *3*: 29-33, 2013.
15 Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, Becker H, Raab HR, Villanueva MT, Witzigmann H, Wittekind C, Beissbarth T and Rödel C: Preoperative *versus* postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol *30(16)*: 1926-1933, 2012.
16 Hoffman JP, Lipsitz S, Pisansky T, Weese JL, Solin L and Benson AB 3rd: Phase II trial of preoperative radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas: an Eastern Cooperative Oncology Group Study. J Clin Oncol *16(1)*: 317-323, 1998.
17 Pisters PW, Abbruzzese JL, Janjan NA, Cleary KR, Charnsangavej C, Goswitz MS, Rich TA, Raijman I, Wolff RA, Lenzi R, Lee JE and Evans DB: Rapid-fractionation preoperative chemoradiation, pancreaticoduodenectomy, and intraoperative radiation therapy for resectable pancreatic adenocarcinoma. J Clin Oncol *16(12)*: 3843-3850, 1998.
18 Staley CA, Lee JE, Cleary KR, Abbruzzese JL, Fenoglio CJ, Rich TA and Evans DB: Preoperative chemoradiation, pancreaticoduode-nectomy, and intraoperative radiation therapy for adenocarcinoma of the pancreatic head. Am J Surg *171(1)*: 118-124, 1996.
19 Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, Padbury R, Moore MJ, Gallinger S, Mariette C, Wente MN, Izbicki JR, Friess H, Lerch MM, Dervenis C, Oláh A, Butturini G, Doi R, Lind PA, Smith D, Valle JW, Palmer DH, Buckels JA, Thompson J, McKay CJ, Rawcliffe CL, Büchler MW and European Study Group for Pancreatic Cancer: Adjuvant chemotherapy with fluorouracil plus folinic acid *vs*. gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA *304(10)*: 1073-1081, 2010.
20 Lawrence TS, Chang EY, Hahn TM, Hertel LW and Shewach DS: Radiosensitization of pancreatic cancer cells by 2',2'-difluoro-2'-deoxycytidine. Int J Radiat Oncol Biol Phys *34(4)*: 867-872, 1996.
21 Talamonti MS, Small W Jr, Mulcahy MF, Wayne JD, Attaluri V, Colletti LM, Zalupski MM, Hoffman JP, Freedman GM, Kinsella TJ, Philip PA and McGinn CJ: A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma. Ann Surg Oncol *13(2)*: 150-158, 2006.
22 Colbert LE, Hall WA, Nickleach D, Switchenko J, Kooby DA, Liu Y, Gillespie T, Lipscomb J, Kauh J and Landry JC: Chemoradiation therapy sequencing for resected pancreatic adenocarcinoma in the National Cancer Data Base. Cancer *120(4)*: 499-506, 2014.
23 Stessin AM, Meyer JE and Sherr DL. Neoadjuvant radiation is associated with improved survival in patients with resectable pancreatic cancer: an analysis of data from the surveillance, epidemiology, and end results (SEER) registry. Int J Radiat Oncol Biol Phys *72(4)*: 1128-1133, 2008.
24 Artinyan A, Anaya DA, McKenzie S, Ellenhorn JD and Kim J: Neoadjuvant therapy is associated with improved survival in resectable pancreatic adenocarcinoma. Cancer *117(10)*: 2044-2049, 2011.
25 Musio D, De Felice F, Bulzonetti N, Guarnaccia R, Caiazzo R, Bangrazi C, Raffetto N and Tombolini V: Neoadjuvant-intensified treatment for rectal cancer: time to change? World J Gastroenterol *19(20)*: 3052-3061, 2013.
26 van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A and CROSS Group: Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med *366(22)*: 2074-2084, 2012.
27 NCT00335543
28 NCT01900327
29 NCT01458717

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