SHORT COMMUNICATION

Does Neoadjuvant Therapy Improve Outcome in Resectable PC? Gastrointestinal Cancers Symposium 2019

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Surgery is associated with improved survival in pancreatic cancer, but unfortunately, even with a successful R0 resection (pathologically negative margin), neither pancreaticoduodenectomy nor distal pancreatectomy, can guarantee a cure and rates of recurrence approach 80%. Whether patients with resectable disease should undergo neoadjuvant treatment (NAT) remains highly controversial. While there are compelling reasons to treat, there is a risk that some patients will not only fail to benefit but progress to unresectable disease. This "failure rate" has been reported to be as high as 16% [1]. A meta-analysis including trials identified by searching MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from 1966 to December 2009 and through reference lists of articles and proceedings of major meetings was performed. A total of 111 studies (n = 4,394) including 56 phase I-II trials were included in this analysis [2]. The data showed that initially resectable pancreatic tumors demonstrated similar resection rate and survival following neoadjuvant therapy compared to those of patients with primary surgical resection of tumors with adjuvant therapy. Another meta-analysis focused on only gemcitabine-based neoadjuvant regimens demonstrated only marginal survival benefits for patients with resectable cancer whether they received radiation or not [3]. In 2017, D'Angelo *et al.* performed one of the first meta- analyses to report survival using ITT analysis. Twelve prospective neoadjuvant studies with both resectable and either borderline resectable and locally advanced PDAC (BR/LA disease), published between 2008 and 2015, were included and the authors reported a resection rate of 65%, and notably, a similar mOS of 22.78 months [4]. More recently, Versteijne *et al.* performed a meta- analysis on pooled data from 38 trials, again using ITT analysis, and included a total of 3,484 patients diagnosed with resectable or BR pancreatic cancer. They reported no meaningful difference in mOS for patients with resectable disease treated with upfront surgery versus neoadjuvant therapy (17.14 v 18.2 months) however, there was a difference in mOS, favoring neoadjuvant therapy over upfront surgery, in patients with BR disease (19.2 v 12.8 months). R0 resection rates favored that receiving neoadjuvant therapy, in both resectable (85% v 71.4%) and BR disease (88.6% v 63.9%) [5]. Similar results were also reported by, Mokdad *et al.* published a unique retrospective study utilizing propensity score matched analysis to investigate the role of neoadjuvant therapy in patients with early stage pancreas cancer. The authors queried the National Cancer Database for patients with stage I or II PDAC who underwent surgery between 2006 and 2012. A total of 2,005 patients treated with neoadjuvant therapy followed by surgery were matched with 6,015 patients who underwent upfront resection and the authors reported a median overall survival difference of 5 months (26 v 21 months) favoring those who received neoadjuvant therapy[6]. Recently , Ivanics *et al.* queried the National Cancer Database for patients with stage I and II body and tail PDAC between 2006-2014, total of 441 patients received neoadjuvant therapy followed by resection (NAT+R) with or without adjuvant therapy(AT) compared to 1323 patient who underwent upfront resection with or without AT. They reported significantly higher median survival in the neoadjuvant group compared to the upfront resection [7]. Datta *et al.* compared long time survival between surgery *vs.* Surgery + AT and NAT + Surgery in a large National Cancer Database and conclude that surgery alone had worse overall survival and no significant difference in overall survival when comparing AT and NAT [8]. Reni M *et al.*. reported on the safety and efficacy of preoperative or postoperative chemotherapy for resectable pancreatic adenocarcinoma (PACT-15), were 88 patients were readmized for adjuvant gemcitabine for six cycles (arm A), six cycles of adjuvant PEXG (cisplatin, epirubicin, and gemcitabine and capecitabine (arm B), or three cycles of PEXG before and three cycles after surgery (arm C) [9]. Cloyd JM, *et al.* compared chemotherapy versus chemoradiation as preoperative therapy for resectable pancreatic cancer using propensity score adjusted analysis and conclude that preoperative CRT is associated with less margin and lymph node positivity, reduced LR, and similar OS compared with preoperative chemotherapy[10]. Neoadjuvant platinum-based chemotherapy with gemcitabine was tested

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in a randomized phase II trial. Patients were randomized to either primary surgery versus neoadjuvant gemcitabine and cisplatin with radiotherapy. Radiotherapy consisted of three-dimensional treatment at 1.8 Gy to 55.8 Gy (tumor) or 50.4 Gy. The target number of patients was 254, however, the study was closed prematurely after 73 patients; with only 66 patients evaluable [11]. The R0 resection rate was 52% (A) and 48% with median OS of 17.4 versus 14.4 months. However, after tumor resection, mOS was 25 *vs.* 18.9 months. [12]

Here we summarize and discuss findings presented at the 2019 Gastrointestinal Cancers Symposium (Abstracts 189, 343, 335, 414, 436, 318, 453, 450, 395, 370, and 409) that relate neoadjuvant therapeutic strategies for resectable pancreatic cancer **(Table 1).**

Based on the above data, a few conclusions can be made. The results of all the studies underline that neoadjuvent therapy seems to improve resectability of tumors that may translate into improved overall survival. The data is promising; however, given the limited sample size, no standardized regimen, subjective variability, no definitive conclusions may be drawn.

In summary, the use of neoadjuvant chemotherapy or chemoradiation in resectable pancreatic cancer remains debatable because of the conflicting data on its effectiveness, and the lack of randomized phase Ⅲ trials to support their use.

Table 1. Summary of results: Neoadjuvant chemotherapies in resectable cancer presented at 2019 ASCO Gastrointestinal Cancers Symposium.

Abstract # Authors	Chemotherapy regimen	Total no. of patients	Surgical resection	R0 resection	Median survival (months)		Study primary endpoint
					Overall	Progression free	
343 Nagai M *et al.*	Retrospective study Full-dose gemcitabine (1000 mg/m^2) with concurrent radiation of 54 Gy	181	129	R0 resection rate and pathological stage were favorable in the NACRT group (p<0.001, p=0.005, p<0.001).	S *vs.* No S (Median survival time: 37.0 *vs.* 27.1 M, p=0.049).	For resected tumors, patients treated with NACRT had a better prognosis than those without in the R and BR-P group (53 *vs.* 36.5 M, p=0.033, 61.7 *vs.* 14.6 M, p=0.002), while NACRT had no significant impact on prognosis in the BR-A group.	NACRT had a variety of favorable impact in PC treatment. In particular, it significantly improved the prognosis in the R and BR-P, but not BR-A.
335 Datta SK *et al.*	Surgically resected AJCC clinical stage 1, 1A, and 1B PAC between 2004-2014 Patients were stratified into 3 groups to assess outcomes • Surgery alone • Surgery+adjuvant therapy (AT) Neoadjuvant therapy (NAT) first followed by surgery	9684	all	N/A	N/A		1. Surgery alone had worse overall survival. 2. There was no significant difference in overall survival when comparing AT and NAT
436 Shahda S *et al.*	Retrospective study • patients received NA CT modified FOLFIRINOX or FOLFIRINOX (59 %), or gemcitabine/ nab-paclitaxel (13%), with XRT in 24 % and completed surgical resection	116 R=47%, BR=53%	ALL		Median OS was 22.5 mo (19.5, 29.8) with <3 mo NA CT versus 16.3 (12.2, 18.9) with ≥ 3 mo NA CT (p=0.02) and was 22.6 mo (17.0, 82.9) with NA CT+XRT versus 19.5 (13.1, 22.5) in NA CT only (p=0.03).	no difference in DFS by duration of NA CT or XRT	patients who received a shorter course of chemotherapy and radiation had improved mOS when calculated from the surgery date
318 Leonard-Murali S *et al.*	The NCDB was queried for Ampullary carcinoma patients with Stage I to III (AAC) who underwent radical surgery. Cohort was separated into NAT followed by surgery and UR (upfront surgery) groups	NAT followed by surgery (47) UR (1521)	all	N/A	No difference in overall survival between the NAT and UR Either as total groups, or when stratified by stage	N/A	Study suggests that a NAT strategy is not preferable to UR for treatment of resectable AAC, regardless of stage

453 Macedo FI *et al*.	The National Cancer Database (NCDB) was queried for patients with stage I-III PDAC who underwent surgical resection from 2004 to 2014 2,351 (75%) patients underwent (NACR) neoadjuvant Chemo radiation and 782 (25%), (NAC) neoadjuvant Chemotherapy alone	3,133	74%		32 months		NACR is associated with lower rates of lymph node positivity, however this did not translate in survival or margin positivity benefit compared to NAC alone
450 Ivanics T *et al*.	National Cancer Database (NCDB) was queried for stage I and II body and tail PDAC Upfront resection group (UR), resection followed by adjuvant therapy (R+AT) And Neoadjuvant therapy followed by resection (NAT+R) And Neoadjuvant therapy followed by resection and adjuvant therapy (NAT+R+AT).	441 patients received NAT+R with or without AT compared to 1323 patient who underwent UR with or without AT	all		Median survival (MS) was higher in the neoadjuvant (NAT+R/ NAT+R+AT) group compared to the upfront resection (UR/ R+AT) group (28.6 *vs.* 22.9 mo) (p<0.001). When further stratified by treatment sequencing the MS was longer in a NAT+R+AT cohort compared to the R+AT group (36.0 *vs.* 25.3 mo)		There appears to be a survival benefit with neoadjuvant systemic therapy in patients with early stage body and tail PDAC. A systemic perioperative treatment sequencing approach (NAT+R+AT) appears to have the greatest survival benefit.
395 Molina G *et al*.	Population-level study evaluated the Spearman correlation between the annual proportion of patients receiving NAT and the annual 1-year and 5-year OS, respectively, using the 2004-2015 National Cancer Database.	18,852 patients	All	9,142 patients	N/A	N/A	This study demonstrates that there is a statistically significant and positive correlation between the proportion of patients with R0/ R1 resected PDAC who received NAT and 1-year OS and 5-year OS, respectively.
370 Zakem S *et al*.	Retrospectively evaluated BRPC and LAPC patients treated with neoadjuvant CT FOLFIRINOX (65%) and gemcitabine/nab-paclitaxel (30%)+SBRT 30-33 Gy in 5	80	53 (79%)	51	24.5 months	DMFS was not significantly different between complete and marked PR compared to those with moderate PR	Neoadjuvant CT+SBRT are associated with favorable PR rates and R0 resection rates
409 MaramaraT *et al*.	National Cancer Database (NCDB) was for patients with PAC who underwent up front surgery (UFS) versus single agent (SAC), or multi agents chemotherapy (MAC) ± RT followed by surgery	(26,563 patients) 23,877 (89.9%) UFS, 1,482 (5.6%) NT+RT (SAC+RT 768, MAC+RT 560), and 1,204 (4.5%) chemo only (SAC 262, MAC 864)			UFS=22.2 mo SAC=23.1 mo MAC=26 mo SAC+RT=27.9 mo MAC+RT=29.8 mo (p<0.001)		Multi-agent CT with or without radiation improves overall survival, R0 resections rates, and complete pathological response rates in patients undergoing neoadjuvant therapy for resectable pancreatic cancer.

189 Unno M *et al.*	Randomized controlled trial Neoadjuvant 2 cycle regimen, gemcitabine at a dose of 1 g/m^2 on D 1 and 8 and oral S-1 at a dose of 40 mg/m^2 B.I.D on 1-14 days Adjuvant S-1 adjuvant for 6 months for patients with curative resection and fully recovered within 10 weeks after surgery in both arms	364	362	The resection rate, R0 resection rate was equivalent in the two groups.	36.7 months in NAC-GS and 26.6 months in Up-S; HR 0.72 (95% confidential interval 0.55-0.94; p=0.015	N/A	The primary endpoint for the phase III part was overall survival (OS)
414 Sohal D *et al.*	Randomized Phase II trial of periop (12 weeks pre-, 12 weeks post-op) CTx with either mFOLFIRINOX (5-fluorouracil, irinotecan, oxaliplatin – without bolus 5-FU and leucovorin; Arm 1), or gemcitabine/nab-paclitaxel (Arm 2).	103	72	N/A			Preop CTx safety and resection rates are encouraging

Conflicts of Interest

The authors report no conflict of interest.

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