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Scientific Article

Treatment strategies and clinical outcomes of locally advanced pancreatic cancer patients treated at high-volume facilities and academic centers

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Abstract

Purpose: Locally advanced pancreatic cancer (LAPC) treatment has varying practice patterns with poor outcomes. We investigated treatment using single-agent chemotherapy and multiagent chemotherapy (MAC) with or without radiation therapy (RT) at high-volume facilities (HVFs) and academic centers (ACs).

Methods and Materials: The National Cancer Database was used to obtain data on 10,139 patients with LAPC. HVF was defined as the top 5% of facilities per number of patients treated at each facility. Univariate and multivariable (MVA) analysis Cox regressions were performed to identify the impact of HVF, AC, MAC, and RT on overall survival (OS).

Results: The median age of patients was 66 years (range, 22-90); 50.1% were male and 49.9% female. Of the patients, 46.1% received MAC, 53.8% received single-agent chemotherapy, 45.7% received RT, 54.3% did not receive RT, and 5% underwent surgical resection. The median follow-up was 48.8 months. On MVA, treatment at HVFs and ACs remained significantly associated with improved OS, with a hazard ratio (HR) of 0.84 ($P < .001$) and 0.94 ($P = .004$), respectively. The median OS for HVF treatment compared with low-volume facilities was 14.3 versus 11.2 months, respectively ($P < .001$). The median OS for AC treatment versus non-AC was 12.1 versus 10.8 months, respectively ($P < .001$). Additionally, on MVA, receipt of RT and MAC remained significantly associated with improved OS (HR: 0.76; $P < .001$; and HR: 0.73; $P < .001$, respectively). MVA for receipt of surgery showed that MAC is a significant predictor for receiving surgery (odds ratio: 1.29; $P = .009$).

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Conclusions: Our results build on a growing literature supporting RT and MAC in treating LAPC. Additionally, we believe that—in the absence of prospective data—this makes a strong case for considering MAC with RT at ACs and HVFs for treating LAPC.

Introduction

Pancreatic cancer (PC) continues to have poor survival rates with only 8% of patients in the United States alive 5 years.[1] Approximately 40% of patients present with locally advanced/unresectable PC (LAPC) but non-metastatic disease. Because of the limited therapeutic options and generally poor prognoses, treatment paradigms that involve chemotherapy, radiation therapy (RT), and surgery are not well established, and practice patterns vary greatly.[2] Type of treatment is further dictated by additional variables such as patient performance status, which often remains poor and adds complexity to management. As a result, care delivered by a multidisciplinary team of medical, RT, and surgical oncologists has been shown to affect treatment decisions.[3]

The resection rates for upfront resectable and LAPC have increased over the past 3 decades, with associated improvement in survival.[4–6] Such improvements have been attributed, in part, to surgery at high-volume facilities (HVFs), likely as a result of higher margin negative resection rates, comprehensive lymph node dissections, lower perioperative mortality, and increased use of adjuvant therapy compared with low volume facilities (LVFs).[7–9] Hospital volume, more than individual surgeon experience, has been associated with improved clinical outcomes, which may be explained by the availability of multidisciplinary management teams at such facilities.[10] A positive correlation has also been shown between hospital volume and survival in patients with metastatic PC who receive palliative chemotherapy.[11] Data with regard to the use of chemotherapy and RT at HVFs and academic centers (ACs) and associated clinical outcomes are lacking.

The use of aggressive chemotherapy regimens has led to improved margin negative resection rates and decreased operative times for LAPC, irrespective of whether treatment was received at HVFs or ACs.[12,13] However, prospective randomized evidence that validates the use of multiagent chemotherapy (MAC) in LAPC remains limited. Given the high likelihood of occult metastatic disease and persistently poor prognosis in these patients, chemotherapy treatment paradigms are extrapolated from stage IV disease.[14,15]

Data on the use of RT in LAPC are mixed, further confounding selection of appropriate therapies. The addition of RT to gemcitabine upfront compared with gemcitabine alone in LAPC resulted in improved survival.[16] Conversely, the LAP-07 study identified no benefit to the addition of chemoradiation therapy to single-agent gemcitabine.[17] Recent retrospective studies have identified higher rates of resection in LAPC receiving RT after MAC,[4] yet practice patterns continue to shift toward use of chemotherapy without RT on the basis of these studies, which do not necessarily reflect contemporary practice patterns.[18]

Given the complex management paradigms of LAPC combined with generally poor outcomes, we investigated the utility of single-agent chemotherapy (SAC) and MAC with or without RT, as well as the potential benefits of treatment at HVFs and ACs.

Methods and Materials

Data base

The National Cancer Database (NCDB) was used to obtain de-identified patient data with institutional review board approval. The NCDB is a registry of data by the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The NCDB obtains cases from more than 1500 facilities, encompassing approximately 70% of new cancers diagnosed in the United States. Established criteria to certify the quality of the submitted data and an application process to obtain the data are outlined by the NCDB. However, upon distribution of the data, the Commission on Cancer of the American College of Surgeons and the American Cancer Society are not responsible for the analysis and interpretation presented herein.

Patient selection

International Classification of Diseases for Oncology-3 codes for PC anatomic site were included (C25.0-C25.9). We excluded all patients with T1 to T3 disease, unknown follow-up, incomplete staging information, noninvasive disease, nonadenocarcinoma histology, or distant metastases at presentation, as well as patients who received radioactive implants, radioisotopes, combination external beam and radioisotopes, radiation type that was not

Table 1 Baseline characteristics, stratified by facility volume and type

Variable	All patients (N = 10139)	Facility volume (95th)			Facility type		
		High (n = 588)	Low (n = 9551)	*P*-value	Academic center (n = 4879)	Non-academic center (n = 5260)	*P*-value
Facility type							
Academic center	4879 (48.12)	588 (100)	4291 (44.93)	**<.001**			
Non-academic center	5260 (51.88)	0 (0)	5260 (55.07)				
Age (y)							
Median (IQR)	66 (58-74)	66 (58-74)	66 (58-74)	.768	65 (58-74)	67 (58-74)	**<.001**
Sex							
Female	5083 (50.13)	279 (47.45)	4804 (50.3)	.180	2423 (49.66)	2660 (50.57)	.361
Male	5056 (49.87)	309 (52.55)	4747 (49.7)		2456 (50.34)	2600 (49.43)	
Race							
Black	1386 (13.81)	74 (12.69)	1312 (13.88)	.670	760 (15.8)	626 (11.98)	**<.001**
Other	316 (3.15)	17 (2.92)	299 (3.16)		177 (3.68)	139 (2.66)	
White	8334 (83.04)	492 (84.39)	7842 (82.96)		3872 (80.52)	4462 (85.36)	
Median income							
<$38,000	1650 (16.67)	79 (13.64)	1571 (16.86)	**<.001**	783 (16.44)	867 (16.88)	**<.001**
$38,000-$47,999	2279 (23.02)	78 (13.47)	2201 (23.62)		927 (19.46)	1352 (26.32)	
$48,000-$62,999	2729 (27.57)	111 (19.17)	2618 (28.09)		1226 (25.74)	1503 (29.26)	
>$63,000	3241 (32.74)	311 (53.71)	2930 (31.44)		1827 (38.36)	1414 (27.53)	
Education							
Low (>21%)	1520 (15.35)	79 (13.64)	1441 (15.45)	**.008**	754 (15.83)	766 (14.9)	**<.001**
13%-20.9%	2481 (25.05)	128 (22.11)	2353 (25.23)		1117 (23.45)	1364 (26.54)	
7%-12.9%	3388 (34.21)	191 (32.99)	3197 (34.28)		1586 (33.29)	1802 (35.06)	
High (<7%)	2515 (25.39)	181 (31.26)	2334 (25.03)		1307 (27.43)	1208 (23.5)	
Charlson-Deyo comorbidity score							
0	7275 (71.75)	399 (67.86)	6876 (71.99)	.096	3545 (72.66)	3730 (70.91)	.148
1	2308 (22.76)	152 (25.85)	2156 (22.57)		1076 (22.05)	1232 (23.42)	
≥2	556 (5.48)	37 (6.29)	519 (5.43)		258 (5.29)	298 (5.67)	
Year of diagnosis							
2004-2006	2230 (21.99)	133 (22.62)	2097 (21.96)	.143	1060 (21.73)	1170 (22.24)	**.042**
2007-2009	2981 (29.4)	152 (25.85)	2829 (29.62)		1387 (28.43)	1594 (30.3)	
2010-2013	4928 (48.6)	303 (51.53)	4625 (48.42)		2432 (49.85)	2496 (47.45)	
Surgery							
Surgery	506 (4.99)	46 (7.82)	460 (4.82)	**.001**	281 (5.76)	225 (4.28)	**<.001**
No surgery	9630 (95.01)	542 (92.18)	9088 (95.18)		4596 (94.24)	5034 (95.72)	
Radiation							
Radiation	4631 (45.68)	220 (37.41)	4411 (46.18)	**<.001**	2071 (42.45)	2560 (48.67)	**<.001**
No radiation	5508 (54.32)	368 (62.59)	5140 (53.82)		2808 (57.55)	2700 (51.33)	
Chemotherapy							
Multiagent	4679 (46.15)	365 (62.07)	4314 (45.17)	**<.001**	2439 (49.99)	2240 (42.59)	**<.001**
Single agent	5460 (53.85)	223 (37.93)	5237 (54.83)		2440 (50.01)	3020 (57.41)	

Abbreviation: IQR = interquartile range.
Data are presented as number of patients (column %) or median (IQR).
P-value is calculated by Wilcoxon rank-sum test for age, and χ^2 or Fisher's exact test for categorical variables, as appropriate.
Bold values that are statistically significant at a *P* value of less than 0.05.

otherwise specified, RT at multiple facilities, RT directed to nonprimary sites, RT administered after surgical resection, or nondefinitive dose of RT. Those who had unknown receipt of chemotherapy, no chemotherapy administered, and unknown AC status were also excluded. Only patients with clinical T4/stage 3 disease were included. Adenocarcinoma histology was defined as 8140-41, 8145, 8154, 8210, 8230, 8255, 8260-62, 8310, 8323, 8440, 8500, 8551, 8560, 8562, and 8570. Patients who received definitive doses of standard fractionated RT (45-65 Gy in 1.8-2 Gy fractions) and stereotactic body RT (21 Gy in 3 fractions or 30-50 Gy in 5 fractions) were included.[19]

Statistical analysis

The primary outcome was overall survival (OS; time from diagnosis to death). Facility volume was calculated

Table 2 Baseline characteristics, stratified by chemotherapy and radiation

Variable	Chemotherapy			Radiation		
	Multiagent (n = 4679)	Single agent (n = 5460)	*P*-value	Radiation (n = 4631)	No radiation (n = 5508)	*P*-value
Age (y)						
Median (IQR)	64 (58-74)	68 (58-74)	**<.001**	65 (58-74)	67 (58-74)	**<.001**
Sex						
Female	2245 (47.98)	2838 (51.98)	**<.001**	2248 (48.54)	2835 (51.47)	**.003**
Male	2434 (52.02)	2622 (48.02)		2383 (51.46)	2673 (48.53)	
Race						
Black	583 (12.59)	803 (14.86)	**<.001**	647 (14.08)	739 (13.58)	**.006**
Other	170 (3.67)	146 (2.7)		117 (2.55)	199 (3.66)	
White	3879 (83.74)	4455 (82.44)		3831 (83.37)	4503 (82.76)	
Median income						
<$38,000	681 (14.88)	969 (18.2)	**<.001**	759 (16.82)	891 (16.54)	.416
$38,000-$47,999	986 (21.55)	1293 (24.29)		1064 (23.58)	1215 (22.56)	
$48,000-$62,999	1239 (27.08)	1490 (27.99)		1211 (26.83)	1518 (28.18)	
>$63,000	1670 (36.49)	1571 (29.51)		1479 (32.77)	1762 (32.71)	
Education						
Low (>21%)	638 (13.93)	882 (16.57)	**<.001**	692 (15.33)	828 (15.36)	.997
13%-20.9%	1083 (23.65)	1398 (26.26)		1135 (25.14)	1346 (24.97)	
7%-12.9%	1610 (35.15)	1778 (33.4)		1544 (34.2)	1844 (34.21)	
High (<7%)	1249 (27.27)	1266 (23.78)		1143 (25.32)	1372 (25.45)	
Charlson-Deyo comorbidity score						
0	3460 (73.95)	3815 (69.87)	**<.001**	3394 (73.29)	3881 (70.46)	**.005**
1	1001 (21.39)	1307 (23.94)		1006 (21.72)	1302 (23.64)	
≥2	218 (4.66)	338 (6.19)		231 (4.99)	325 (5.9)	
Year of diagnosis						
2004-2006	842 (18)	1388 (25.42)	**<.001**	1209 (26.11)	1021 (18.54)	**<.001**
2007-2009	1153 (24.64)	1828 (33.48)		1449 (31.29)	1532 (27.81)	
2010-2013	2684 (57.36)	2244 (41.1)		1973 (42.6)	2955 (53.65)	
Surgery						
Surgery	296 (6.33)	210 (3.85)	**<.001**	238 (5.14)	268 (4.87)	.533
No surgery	4382 (93.67)	5248 (96.15)		4393 (94.86)	5237 (95.13)	
Radiation						
Radiation	1927 (41.18)	2704 (49.52)	**<.001**			
No radiation	2752 (58.82)	2756 (50.48)				

Abbreviation: IQR = interquartile range.
Data are presented as number of patients (column %) or median (IQR).
P-value is calculated by Wilcoxon rank-sum test for age, and χ^2 or Fisher's exact test for categorical variables, as appropriate.
Bold values that are statistically significant at a *P* value of less than 0.05.

as the number of patients treated per facility, and HVFs represented the top 5% of facilities in the cohort. Primary predictor variables were chemotherapy, RT, facility volume, and facility type. Univariate associations between variables were examined with Wilcoxon rank-sum test, χ^2 test, or Fisher's exact test, where appropriate. A logistic regression model was employed to identify variables associated with the receipt of surgery. Median follow-up was calculated using the reverse Kaplan-Meier method.[20] Survival functions were estimated with the Kaplan-Meier method and compared using a log-rank test.[21]

Univariate and multivariable survival analyses were conducted with a Cox proportional hazards model.[22] Multivariable analyses (MVAs) were performed using a stepwise variable selection procedure based on the Akaike information criterion.[23] The final multivariable models were returned by the lowest Akaike information criterion value. In the MVA, the possibility of multicollinearity was assessed by tolerance and the variance inflation factor. The proportional hazards assumption was assessed graphically and analytically with scaled Schoenfeld residuals.[24] A violation of the proportional hazards assumption was addressed by use of a stratified Cox regression model. The analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC) and R package version 3.4.1 with 2-sided tests and a significance level of .05.

Table 3 Univariate and multivariable analyses of overall survival

Variable	Univariate			Multivariable	
	N	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Facility volume (95th percentile)					
High	588	0.75 (0.69-0.82)	**<.001**	0.84 (0.76-0.92)	**<.001**
Low	9551	1 (Reference)		1 (Reference)	
Facility type					
Academic center	4879	0.87 (0.83-0.91)	**<.001**	0.94 (0.90-0.98)	**.004**
Non-academic center	5260	1 (Reference)		1 (Reference)	
Radiation					
Radiation	4631	0.79 (0.76-0.83)	**<.001**	0.76 (0.73-0.80)	**<.001**
No radiation	5508	1 (Reference)		1 (Reference)	
Chemotherapy					
Multiagent	4679	0.68 (0.66-0.71)	**<.001**	0.73 (0.70-0.76)	**<.001**
Single agent	5460	1 (Reference)		1 (Reference)	
Age (y)	10139	1.01 (1.01-1.01)	**<.001**	1.01 (1.00-1.01)	**<.001**
Sex					
Female	5083	0.98 (0.94-1.02)	.265	0.94 (0.91-0.99)	**.008**
Male	5056	1 (Reference)		1 (Reference)	
Race			**.001***		**<.001***
Black	1386	0.94 (0.88-1.00)	**.034**	0.86 (0.81-0.92)	**<.001**
Other	316	0.83 (0.73-0.93)	**.002**	0.82 (0.73-0.93)	**.002**
White	8334	1 (Reference)		1 (Reference)	
Median income			**<.001***		**<.001***
<$38,000	1650	1.27 (1.19-1.35)	**<.001**	1.25 (1.17-1.34)	**<.001**
$38,000-$47,999	2279	1.15 (1.09-1.22)	**<.001**	1.09 (1.02-1.15)	**.005**
$48,000-$62,999	2729	1.18 (1.12-1.24)	**<.001**	1.14 (1.08-1.20)	**<.001**
>$63,000	3241	1 (Reference)		1 (Reference)	
Education			**<.001***		
Low (>21%)	1520	1.12 (1.05-1.20)	**<.001**	†	
13%-20.9%	2481	1.15 (1.08-1.22)	**<.001**		
7%-12.9%	3388	1.09 (1.03-1.15)	**.002**		
High (<7%)	2515	1 (Reference)			
Charlson-Deyo comorbidity score			**<.001***		**.028***
0	7275	0.85 (0.78-0.93)	**<.001**	0.90 (0.82-0.98)	**.021**
1	2308	0.91 (0.82-1.00)	**.046**	0.94 (0.85-1.03)	.191
≥2	556	1 (Reference)		1 (Reference)	
Year of diagnosis			**<.001***		**<.001***
2004-2006	2230	1.27 (1.21-1.34)	**<.001**	1.21 (1.14-1.27)	**<.001**
2007-2009	2981	1.26 (1.20-1.32)	**<.001**	1.16 (1.11-1.22)	**<.001**
2010-2013	4928	1 (Reference)		1 (Reference)	
Surgery					
Surgery	506	0.40 (0.36-0.45)	**<.001**	0.43 (0.38-0.48)	**<.001**
No surgery	9630	1 (Reference)		1 (Reference)	

Abbreviation: CI = confidence interval.
A total of 9795 observations were used in the multivariable model.
Bold values that are statistically significant at a *P* value of less than 0.05.
* Overall *P*-value for categorical variables with more than 2 levels.
† Variables dropped out of the model.

Results

Patient characteristics

Between 2004 and 2014, 309,697 patients with PC were identified. After applying the exclusion criteria, 10,139 patients remained, of whom 4679 (46.1%) received MAC, 5460 (53.8%) received SAC, 4631 (45.7%) received RT, and 506 (5%) underwent surgical resection (Tables 1 and 2). Additional baseline characteristics, demographics, and univariate association of facility volume and academic status can be found in Tables 1 and 2. The median follow-up was 48.8 months (95% confidence interval [CI], 46.0-52.1 months). Using

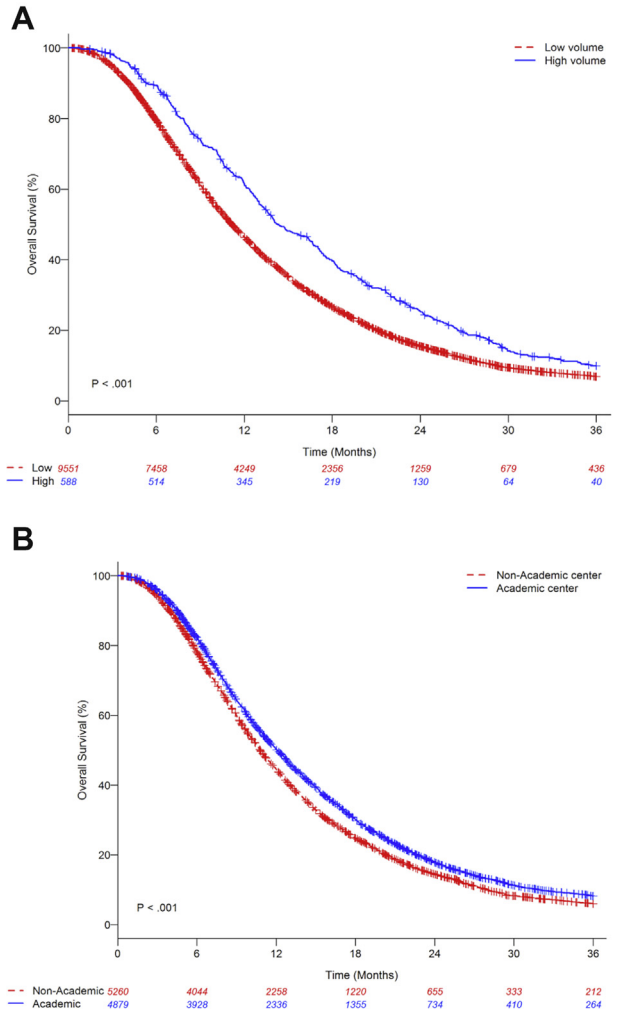

Fig. 1 (A) Kaplan-Meier estimates of overall survival probability, stratified by facility volume. Low-volume facility (red dotted line) and high-volume facility (blue solid line). (B) Kaplan-Meier estimates of overall survival probability, stratified by facility type. Nonacademic center (red dotted line) and academic center (blue solid line). Note: Curves are limited up to 36 months.

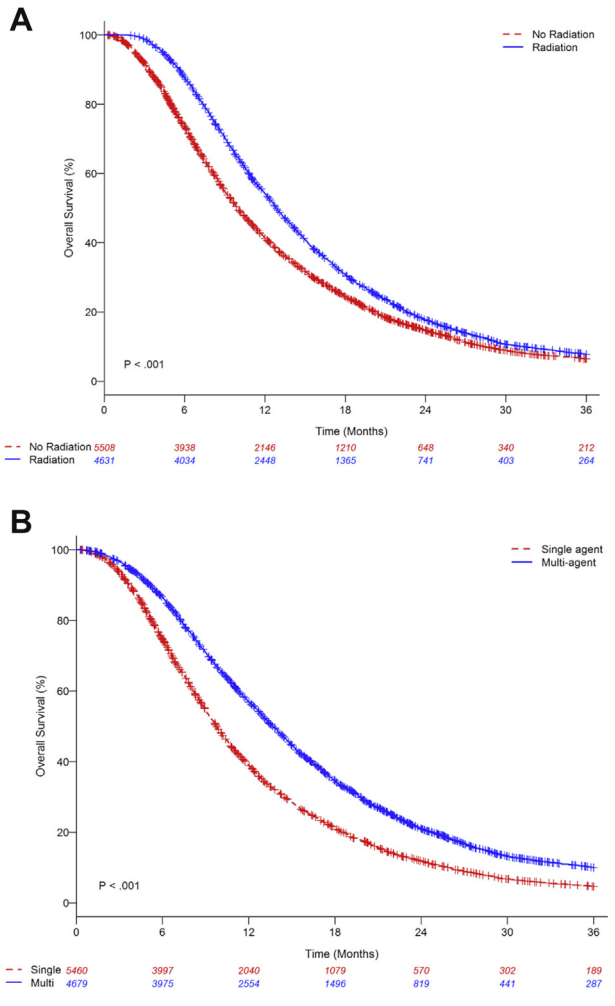

Fig. 2 (A) Kaplan-Meier estimates of overall survival probability, stratified by radiation. No radiation (red dotted line) and radiation (blue solid line). (B) Kaplan-Meier estimates of overall survival probability, stratified by type of chemotherapy. Single-agent (red dotted line) and multiagent (blue solid line) chemotherapy. Note: Curves are limited up to 36 months.

an HVF cutoff of 95%, 88% of ACs and 100% of non-ACs were identified as LVFs.

Univariate analyses and MVAs for association with OS are provided in Table 3. The multivariable model was further presented as the nomogram in the Appendix (available online at https://dx.doi.org/10.1016/j.adro.2018.10.006). A significant association between treatment at HVFs and median income, education, AC status, and receipt of surgery, RT, and chemotherapy was identified on univariate analysis (Table 1). Treatment at an AC was also significantly associated with patient age, race, median income, education, year of diagnosis, and treatment with surgery, RT, and chemotherapy (Table 1). After adjusting for age, sex, race, median income, comorbidity score, year of diagnosis, RT, chemotherapy, and surgery, treatment at an HVF and AC remained independently associated with improved OS, with a hazard ratio (HR) of 0.84 (95% CI, 0.76-0.92; $P < .001$) and 0.94 (95% CI, 0.90-0.98; $P = .004$), respectively (Table 3).

Treatment at HVFs and ACs, receipt of RT, and MAC were significantly associated with improved OS on univariate analysis ($P < .001$; Table 3). Median OS for patients treated at an HVF versus LVF was 14.3 versus 11.2 months ($P < .001$; Fig. 1A). Median OS for patients treated at ACs compared with non-ACs was 12.1 versus 10.8 months ($P < .001$; Fig. 1B). Receipt of RT and MAC remained independently associated with improved OS (HR: 0.76; 95% CI, 0.73-0.80; $P < .001$; and HR: 0.73; 95% CI, 0.70-0.76; $P < .001$, respectively) on MVA. Median OS for patients who received RT compared with no RT was 12.9 versus 9.9 months ($P < .001$; Fig. 2A), and that for patients who received MAC compared with SAC was 13.7 versus 9.8 months ($P < .001$; Fig. 2B).

Table 4 Univariate and multivariable analyses of receipt of surgical resection

Variable	Univariate			Multivariable	
	N	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Facility volume (95th percentile)					
High	588	1.68 (1.22-2.30)	.001	1.34 (0.95-1.88)	.093
Low	9548	1 (Reference)		1 (Reference)	
Facility type					
Academic center	4877	1.37 (1.14-1.64)	<.001	1.21 (0.99-1.46)	.057
Non-academic center	5259	1 (Reference)		1 (Reference)	
Radiation					
Radiation	4631	1.06 (0.89-1.27)	.533	†	
No radiation	5505	1 (Reference)			
Chemotherapy					
Multiagent	4678	1.69 (1.41-2.02)	<.001	1.29 (1.06-1.56)	.009
Single agent	5458	1 (Reference)		1 (Reference)	
Age (y)	10136	0.97 (0.96-0.98)	<.001	0.97 (0.96-0.98)	<.001
Sex					
Female	5081	0.90 (0.75-1.08)	.249	†	
Male	5055	1 (Reference)			
Race			.004*		.006*
Black	1386	0.59 (0.43-0.80)	<.001	0.59 (0.42-0.82)	.002
Other	316	0.95 (0.57-1.59)	.850	0.83 (0.49-1.39)	.476
White	8331	1 (Reference)		1 (Reference)	
Median income			<.001*		.009*
<$38,000	1650	0.63 (0.47-0.83)	.001	0.72 (0.53-0.98)	.035
$38,000-$47,999	2278	0.61 (0.47-0.79)	<.001	0.67 (0.51-0.87)	.003
$48,000-$62,999	2729	0.86 (0.69-1.08)	.191	0.94 (0.75-1.17)	.559
>$63,000	3239	1 (Reference)		1 (Reference)	
Education			.001*		
Low (>21%)	1519	0.54 (0.39-0.75)	<.001	†	
13%-20.9%	2481	0.75 (0.58-0.96)	.022		
7%-12.9%	3387	0.89 (0.71-1.11)	.298		
High (<7%)	2514	1 (Reference)			
Charlson-Deyo comorbidity score			.939*		
0	7272	1.07 (0.71-1.61)	.731	†	
1	2308	1.08 (0.70-1.67)	.733		
≥2	556	1 (Reference)			
Year of diagnosis			<.001*		<.001*
2004-2006	2229	0.52 (0.40-0.67)	<.001	0.55 (0.42-0.71)	<.001
2007-2009	2980	0.53 (0.43-0.67)	<.001	0.54 (0.43-0.68)	<.001
2010-2013	4927	1 (Reference)		1 (Reference)	

Abbreviation: CI = confidence interval.

A total of 9795 observations were used in the multivariable model.

* Overall *P*-value for categorical variables with more than 2 levels.

† Variables dropped out of the model.

After adjusting for facility volume, facility type, age, race, median income, and year of diagnosis, MAC was independently associated with surgical resection on MVA (odds ratio [OR]: 1.29; 95% CI, 1.06-1.56; $P = .009$; Table 4). Low-income patients, African Americans, and patients treated before 2010 were less likely to undergo surgery ($P < .05$). RT was not associated with surgical resection ($P = .533$). There was a trend suggesting a higher likelihood of surgical resection at HVFs and ACs, but this was not significant (OR: 1.34; 95% CI, 0.95-1.88; $P = .093$; and OR: 1.21; 95% CI, 0.99-1.46; $P = .057$, respectively).

In the small cohort of patients with LAPC who underwent surgery (5%), treatment with neoadjuvant RT (HR: 0.71; 95% CI, 0.57-0.88; $P = .002$) and MAC (HR: 0.80; 95% CI, 0.64-0.99; $P = .043$) was independently

Table 5 Univariate and multivariable analyses of overall survival in surgically resected patients

Variable	Univariate			Multivariable	
	N	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Facility volume (95th percentile)					
High	46	0.93 (0.65-1.33)	.701	†	
Low	460	1 (Reference)			
Facility type					
Academic center	281	1.01 (0.82-1.25)	.912	†	
Non-academic center	225	1 (Reference)			
Radiation					
Radiation	238	0.72 (0.59-0.89)	**.002**	0.71 (0.57-0.88)	**.002**
No radiation	268	1 (Reference)		1 (Reference)	
Chemotherapy					
Multiagent	296	0.71 (0.57-0.87)	**.001**	0.80 (0.64-0.99)	**.043**
Single agent	210	1 (Reference)		1 (Reference)	
Age (y)	506	1.01 (1.00-1.02)	**.025**	1.01 (1.00-1.02)	.084
Sex					
Female	241	0.89 (0.72-1.10)	.282	†	
Male	265	1 (Reference)			
Race			.900*		
Black	44	1.00 (0.69-1.45)	.999	†	
Other	16	0.84 (0.40-1.78)	.647		
White	442	1 (Reference)			
Median income			.986*		
<$38,000	65	1.03 (0.73-1.46)	.861	†	
$38,000-$47,999	87	1.06 (0.78-1.42)	.719		
$48,000-$62,999	146	1.03 (0.80-1.33)	.815		
>$63,000	199	1 (Reference)			
Education			.943*		
Low (>21%)	51	0.90 (0.60-1.35)	.619	†	
13%-20.9%	113	1.03 (0.77-1.38)	.856		
7%-12.9%	182	1.01 (0.78-1.30)	.946		
High (<7%)	151	1 (Reference)			
Charlson-Deyo comorbidity score			**<.001***		**<.001***
0	364	0.45 (0.29-0.68)	**<.001**	0.41 (0.26-0.62)	**<.001**
1	116	0.38 (0.24-0.60)	**<.001**	0.35 (0.22-0.56)	**<.001**
≥2	26	1 (Reference)		1 (Reference)	
Year of diagnosis			**<.001***		
2004-2006	78	1.73 (1.30-2.28)	**<.001**	‡	
2007-2009	107	1.40 (1.10-1.80)	**.007**		
2010-2013	321	1 (Reference)			

Abbreviation: CI = confidence interval.
A total of 506 observations were used in the multivariable model.
Bold values that are statistically significant at a *P* value of less than 0.05.
* Overall *P*-value for categorical variables with more than 2 levels.
† Variables dropped out of the model.
‡ Model was stratified on year of diagnosis due to nonproportional hazard.

associated with improved OS (Table 5). The median OS of surgically resected patients who received neoadjuvant MAC versus SAC was 25.3 versus 20.7 months ($P = .002$; Fig. 3A). The median OS for surgically resected patients receiving RT versus no RT was 25.6 versus 19.4 months ($P = .001$; Fig. 3B). Moreover, surgically resected patients who received neoadjuvant RT were more likely to have a margin negative resection (80.4% vs 66.9%; $P < .001$; Table 6).

Discussion

To our knowledge, this is the first study to identify significant associations between treatment at an HVF or AC and receipt of MAC or RT and improved OS in LAPC. These data expand on published surgical series of PC, which identified improvements in postoperative mortality rates and OS at HVFs and ACs.[25–27] Similarly,

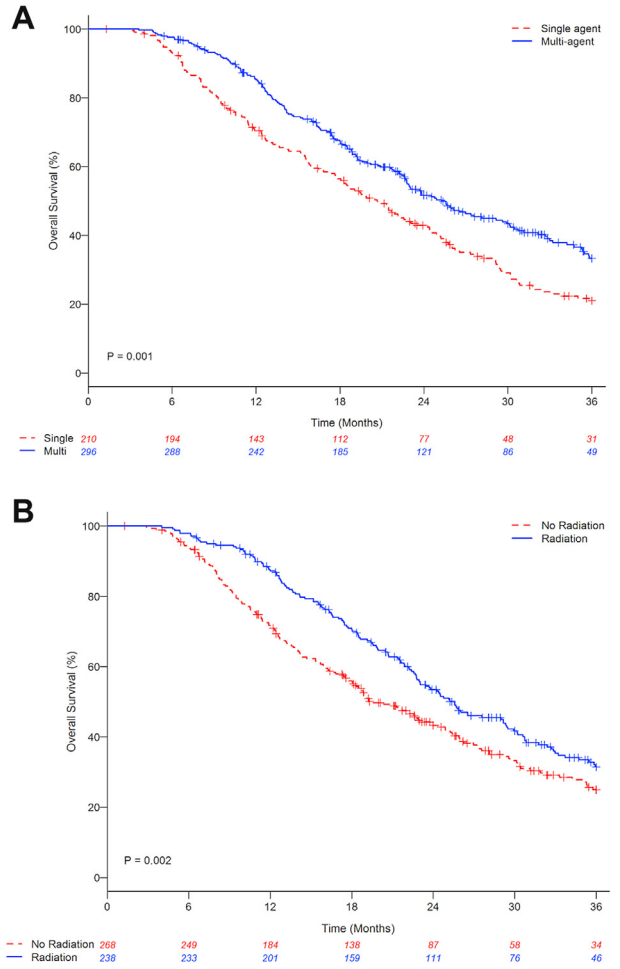

Fig. 3 (A) Kaplan-Meier estimates of overall survival probability, stratified by type of neoadjuvant chemotherapy in resected patients. Single-agent (red dotted line) and multiagent (blue dotted line) chemotherapy. (B) Kaplan-Meier estimates of overall survival probability, stratified by neoadjuvant radiation in resected patients. No radiation (red dotted line) and radiation (blue solid line). Note: Curves are limited up to 36 months.

surgical volumes have a significant impact on clinical outcomes after major surgical procedures.[28,29] These studies were conducted on treatment-naïve patients with resectable PC, with limited chemotherapy- and RT-relevant data provided on the small subset of included patients with LAPC. Yet, variables such as specialized postoperative intensive care units, increased use of adjuvant care, and dedicated ancillary care services were more likely to be provided at HVFs and ACs, and these findings may be applied to the current study.[6–9,28,29] The use of multidisciplinary clinics at HVFs and ACs have led to changes in PC treatment recommendations in almost 25% of patients, likely because of subspecialized surgical, radiation, and medical oncology care.[3,30] Patients with LAPC who were treated at HVFs and ACs likely had improved access to specialized care given the association of treatment patterns with income, education, and age at the time of diagnosis.

Table 6 Margin status in resected patients

Variable	Radiation	No radiation	*P*-value
Surgical margins			
Residual tumor	44 (19.56)	80 (33.06)	**<.001**
No residual tumor	181 (80.44)	162 (66.94)	

Data are presented as number of patients (column %).
P-value is calculated by χ^2 test.
Bold values that are statistically significant at a *P* value of less than 0.05.

Treatment with MAC was independently associated with improved survival in LAPC compared with SAC. Prospective data are yet to be reported on the benefit of MAC in LAPC. Our data support the findings of other limited retrospective series and meta analyses that investigated the use of multiagent regimens in LAPC.[31] Interestingly, MAC was more likely to be administered at HVFs, and SAC was more likely to be given at ACs, suggesting evolving adaptation of metastatic treatment paradigms to LAPC. The use of MAC significantly improves clinical outcomes in metastatic PC, yet its use is associated with significant toxicities.[32] Despite this, intensive medical management of treatment-related side effects[32] can lead to improved quality of life, shorter lengths of hospital stay, and improved survival.[33–37]

However, such supportive care measures may be of limited availability in a community setting.[38] Haj Mohammad et al.[11] recently reported on the use of palliative chemotherapy for metastatic PC in the Netherlands. Patients diagnosed and treated at HVFs and patients treated at LVFs had an HR for OS of 0.74 and 0.76, respectively.[11] Despite this seemingly clinical benefit, only 24% of patients received any form of systemic therapy, likely because of the conservation of community resources in what is widely considered to be a universally terminal disease. Additionally, adaptation of metastatic treatment paradigms to LAPC may be delayed in the community setting and more readily adopted by ACs and HVFs.[18,39,40] When using an HVF cut point of 95%, the vast majority of ACs and all non-ACs were considered LVFs, highlighting not only the relative rarity of this disease, but also the absolute number of PC treatment centers of excellence.

Similar to MAC, RT was independently associated with improved OS in LAPC after adjusting for covariates, including facility type, facility volume, and type of chemotherapy. Although the benefit of RT was seen irrespective of whether SAC or MAC was received, RT was administered after chemotherapy, which likely indicates the selection of patients who did not progress on systemic therapy.

Interestingly, RT was less likely to be administered at an HVF or AC compared with LVF or non-AC,

respectively. This may be because of the recently reported but criticized LAP 07 study, which reported no benefit when concurrent chemoradiation was added to single-agent gemcitabine. The criticisms relate to the use of an SAC backbone, which is unlikely to provide durable control of micrometastatic disease, and the seemingly lofty clinical endpoint of 3-month improvement in median OS. In this setting, the potential survival benefit associated with improved locoregional control is likely mitigated by inferior systemic control.[17] Lack of RT quality assurance also likely contributed to the lack of benefit seen with RT in the LAP 07 study.

Despite the increasing incidence of PC, the absolute number of patients seen annually per treating radiation oncologist are likely low, yet the complexity associated with incorporation of techniques such as intensity modulated RT (IMRT) and image guided treatments remains high.[18] IMRT has reduced toxicities, improved local control, and increased survival compared with less conformal techniques.[41,42] The clinical benefits associated with IMRT are likely driven by the ability to provide higher RT doses, downstaging, and margin negative resections, which is consistent with the results of our study.[42,43] Treatment at an HVF or AC may be more likely to involve peer review of treatment plans, which can lead to improvements in clinical care.[44] Taken together, the increased subspecialized care likely to be received at an HVF and/or AC may help account for these clinical benefits.

Although there was a trend toward increased rates of surgical resection at HVFs and ACs, this was not significant. Moreover, the median OS of patients who underwent surgery was similar between HVFs/ACs and LVFs/non-ACs, respectively. Previous studies have shown a clear benefit of resection performed at HVFs by high-volume surgeons,[5,6,10,25,28] but the absolute percentage of patients who underwent resection in this study was low, suggesting the clinical benefits seen in LAPC were largely a result of chemotherapy and RT received at an HVF or in a multidisciplinary setting.

Similar to other studies, patients who received MAC were more likely to undergo surgical resection and had improved OS compared with those who did not undergo resection.[40,45] RT did not increase the likelihood of surgical resection, but the rate of margin negative resection and OS were significantly higher in this cohort, likely highlighting the challenges associated with correct interpretation of computed tomography and magnetic resonance imaging post-RT.[46]

It is possible that PC patients who live in rural areas may not have the capacity to be treated at HVFs or ACs, thereby introducing selection bias into our results. Additionally, low-income, low-education, and African-American patients were more likely to be treated at LVFs or non-ACs. Given the potential benefits associated with treatment of PC at HVFs/ACs, intensive efforts should be made to address such health and economic disparities.[47] Patients with a deeper understanding of their disease may be more motivated to seek treatment at an HVF or AC. This presents a potential confounder but remains challenging to objectively assess using the NCDB.

Performance status data were not available in this study and may introduce selection bias in favor of healthier patients receiving more aggressive treatments such as MAC and RT. Although there is limited data in support of the correlation between comorbidity indices and performance status measures, the former seems to be a stronger predictor of toxicity and clinical outcomes and was used in the present study.[48,49] Nevertheless, the lack of patient performance status and cutoff value for establishing HVF versus LVF was somewhat arbitrary, yet consistent with similar studies in other cancer types.[50,51] The actual cutoff point is perhaps less relevant to the inherent conclusions that suggest that higher PC treatment volumes and physician experience independently contribute to improved clinical outcomes.

Conclusions

To our knowledge, this is the first study to suggest improved survival rates in patients with LAPC treated at HVFs and ACs. The significance of these findings is further highlighted by the dismal prognosis of this devastating disease and the small incremental benefits afforded by new treatments identified over the last 3 decades.

Supplementary Data

Supplementary material for this article can be found at https://dx.doi.org/10.1016/j.adro.2018.10.006.

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