Locally advanced pancreatic cancer in a socio-economically challenged population

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Background Locally advanced pancreatic cancer (LAPC) is associated with poor outcome, and clinical trials are imperative to address this. However, barriers to trial enrollment often exist, particularly in socio-economically challenged populations.

Objective To evaluate the outcome of socio-economically challenged patients who had LAPC, multiple comorbidities, and who were not enrolled on clinical trials, but who were treated with the best standard-of-care.

Methods We retrospectively reviewed the charts of 32 patients diagnosed as having LAPC who were referred to an urban cancer center between 2005 and 2010, analyzing the treatment and outcomes of 19 who underwent treatment at our center.

Results In all 26.3% of the analyzed patients had commercial insurance, 31.6% did not identify English as their preferred language, and 84.2% had ≥ 3 comorbidities. The median overall survival was 19.1 months, with estimated 1- and 2-year survivals of 60.8% and 36.5%, respectively. The median survival for patients receiving chemotherapy followed by chemoradiation was 26.6 months. Toxicities were controllable. Translation services were required by 26% and social services interventions by 84%. Survival analysis based on insurance coverage did not show a significant association with levels of reimbursement.

Limitations Retrospective study, small sample size, differences in chemotherapy types.

Conclusions These patients, representative of a diverse and socio-economically challenged community, were able to receive standard-of-care therapies with acceptable toxicity and to achieve survivals comparable with clinical trials. This was achieved with intense supportive services.

Pancreatic cancer is the fourth most common cause of cancer-related death in the US.[1] For the approximately 30% of patients who present with regional or locally advanced disease[2] (LAPC), the median survival is 6-10 months.[3] Different therapeutic approaches have been advocated, including chemotherapy (CT) and/or chemoradiation (CRT); however, the optimal therapy is not yet well defined.

However, the published survival data for LAPC may be biased by the type of patient enrolled on clinical trials. In general, results from clinical trials reflect the outcomes of patients who were not only "well enough" to fulfill the eligibility criteria, but who also had the social support systems in place to allow them to actively participate in treatment. Most clinical trials exclude patients with high-risk comorbidities, which therefore also exclude a substantial portion of older patients. In addition to the barriers of socio-economic challenges, comorbidities, and older age, additional impediments to standard treatment are related to health insurance.[4-7] It has been suggested that at least some of these barriers may be overcome by treatment at a National Cancer Institute (NCI)-designated cancer center.[8]

Our institution, in the borough of Brooklyn, New York City, serves a heterogeneous patient population from a variety of ethnic backgrounds. Many of our patients are socio-economically challenged, have multiple comorbidities, and are relatively elderly. The purpose of this study was to evaluate these outcomes of LAPC in our disadvantaged population and compare this outcome with those reported in published clinical trials.

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Materials and methods

The Maimonides Medical Center and The University of Medicine and Dentistry of New Jersey institutional review boards approved the retrospective analysis of the records of 89 patients with pancreatic adenocarcinoma who were referred to Maimonides Cancer Center between July 2005 and October 2010. Of the 83 patients whose records included sufficient data to determine the extent of their disease, 32 (38.6%) met the criteria for LAPC (histologically confirmed pancreatic adenocarcinoma, no evidence of distant metastases by thoracoabdominal-pelvic computed tomography scan, and had unresectable tumors). Of those 32 patients, 13 either declined definitive treatment or did not return for care, thus leaving 19 patients for this analysis. Treatment algorithms are shown in Figure 1, and treatment regimens are summarized in Table 1. In general, treatment strategies following the National Comprehensive Cancer Network guidelines were used at the physician's discretion, and supportive care strategies were those used as the standard to address toxicity of treatment.

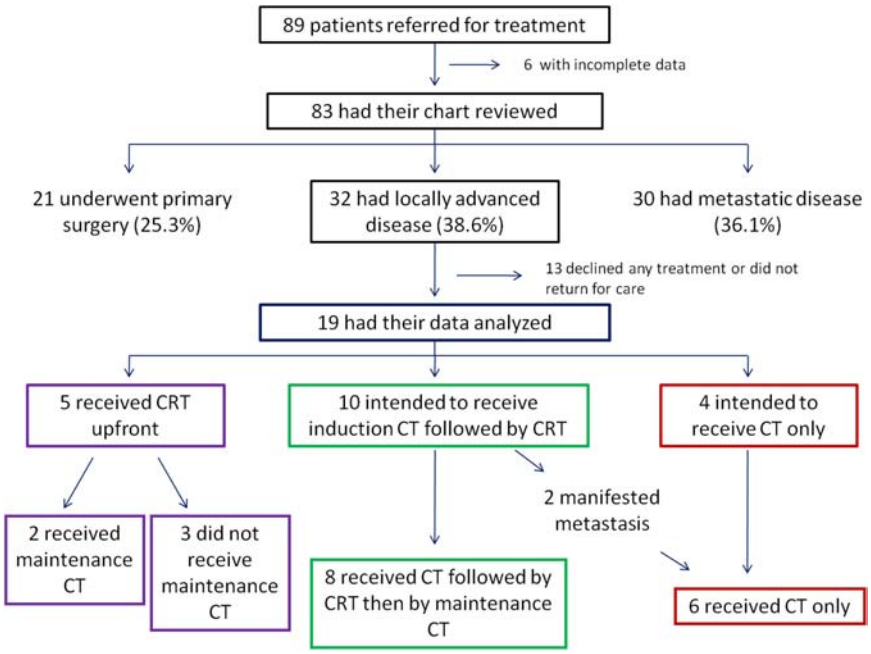

FIGURE 1 Algorithm of patient treatment in the current study. Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy.

Chemotherapy

For the patients receiving induction CT, most (62.5%) received it for 2 to 4 months, depending on tolerability and response. CRT consisted of weekly gemcitabine (69.2%), capecitabine (2.1%) on days of radiotherapy (RT), or 5-FU (7.7%) as continuous infusion. Chemotherapy dose adjustments were based on previously published criteria.

Radiotherapy

RT was delivered with megavoltage photons using 3D techniques (usually 4 fields) and conventional fractionation. All patients underwent computed tomography simulation fused with a PET and/or diagnostic computed tomography scan. The primary tumor and draining lymph nodes were treated to 45 Gy in 25 fractions at 1.8 Gy daily. This was followed by a boost to the primary tumor and gross adenopathy for an additional 5.40 Gy in 3 fractions for a total dose of 50.40 Gy in 28 fractions.

Evaluation and endpoints

Follow-up visits were at least every 1 to 2 months for the first year. Computed tomography scans were obtained every 3 to 4 months, or when a significant change in clinical status was noted. Overall survival, the primary endpoint, was analyzed with respect to treatment modality, charges and corresponding reimbursements. Local and distant progression was determined based upon diagnostic radiology review of the images. Evidence of progression at the primary site was considered local progression, and at distant sites (peritoneal, liver, lung, and other systemic metastases) as metastatic progression. Therapy was individualized at the time of progression.

Statistical analysis

Clinical outcomes were evaluated and survival was calculated from the date of pathologic diagnosis to the date of death or to October 1st, 2010 (censoring date). Survivals by different treatment modalities and cost analysis based on type of insurance were examined using the Kaplan-Meier (K-M) method.

Results

Patient characteristics are shown in Table 2. In all, 42.1% of our patients were aged 70 years or more, and 84% had 3 or more comorbidities. Minority groups were represented by 42.1% of our patients, with equal proportions of African-American and Asians (15.8%); 10.5% were Hispanic. Five of the 19 patients received CRT upfront. Ten received induction CT and were meant to then receive CRT, but as 2 of them progressed with metastases during the induction phase, they continued receiving CT (6 patients; Figure 1). Thus, 8 patients received induction CT followed by concurrent CRT.

TABLE 1 Summary of treatment regimens

Treatment modalities	Regimens
CRT upfront followed by maintenance CT	Single agent – gemcitabine[10] Doublet – gemcitabine and capecitabine[9]
CT only	Single agents – gemcitabine,[10] docetaxel,[11] or capecitabine[12] Doublet – GEMOX[13]
Induction CT followed by CRT	
Induction, 2-4 mo	Single agent – gemcitabine[10] Combinations – GEMOX,[13] Nordic FLOX,[14] Nordic FLOX and bevacizumab,[14,15] FOLFIRI.3,[17] gemcitabine and erlotinib[16]
Maintenance and salvage chemotherapy after CRT	Single agents – gemcitabine,[10] capecitabine[12] Combinations – FOLFIRI.3 and bevacizumab,[15,17] FOLFIRI.3,[17] gemcitabine and nab-paclitaxel,[18] gemcitabine and capecitabine,[9] FOLFOX6[19]

Abbreviations: CRT, chemo-radiation; CT, chemotherapy; nab-paclitaxel, nanoparticle albumin-bound paclitaxel.

Survival

For the group as a whole, the median OS was 19.1 months (95% CI. 10.6-28.5), with 1- and 2-year survivals of 60.8% and 36.5%, respectively (Figure 2C). For the cohort receiving CT followed by CRT, median OS was 26.6 months with 1-year and 2-year survival of 87.5% and 56.2%, respectively; those treated with CT-only and CRT upfront had median OS of 13.8 and 9 months, respectively (Figure 2A). Of the 13 patients who received CRT, 5 experienced local progression, 4 developed metastases, 3 were lost to follow up, and one (from the CRT upfront cohort) ultimately underwent resection of his primary. In the CT-only cohort, 2 patients experienced local progression, 2 metastatic progression, one stable disease, and one was lost to follow up.

Toxicity

CT was in general well tolerated with no grade 5 toxicities. Of the 13 patients receiving CRT, only 1 was not able to tolerate the full course due to grade 4 diarrhea and weakness.

Cost analysis and socio-economic limitations

Three different groups were defined based on the level of reimbursement for charges: Medicaid and Medicaid-HMO (20% and 22% of reimbursements, 5 patients), Medicare and Medicare-HMO (30% and 32% reimbursements, 9 patients), and commercial insurance (42% reimbursement, 5 patients), as shown in Figure 2B. In our geographical region, the commercial insurances have a rate of reimbursement of 42% of the charges. Most of our patients had Medicare and Medicare-HMO coverage (47.4%, Table 2), and 26.3% had Medicaid or Medicaid-HMO insurance coverage. Only 26.3% of them had commercial insurance coverage, as compared to 57% in the published cost analysis of pancreatic carcinoma treatment[20] or to 35.6% in the 1998-2004 US National Cancer Database.[21] Although the numbers were small, there does not appear to be a difference in survival based on insurance coverage (Figure 2B).

Our patients had substantial socio-economic limitations. Translation assistance was provided to 26% of them with Chinese, Spanish, and Russian identified as the most frequent preferred languages of our patients. Almost all (84%) our patients needed social services interventions for financial support in order to provide them with assistance at home and/or with transportation during the course of treatment.

Discussion

To our knowledge, the current study is the first to analyze systemicatically the treatment outcomes of a socio-economically challenged population and compare these outcomes with those achieved by patients enrolled on clinical trials. Our cancer center population hails predominantly from the lower socioeconomic strata, is elderly, has multiple comorbidities, represents minority and ethnically diverse backgrounds, and has limited English proficiency. Despite these challenges, the median survival of 19.1 months of our patients with LAPC is comparable with recently clinical trials which report a median survival of 6.8-15.0 months.[22-28] Limitations of our study include those generally related to retrospective studies, including small sample size, physician bias in the selection of treatment, and the exclusion of patients whose challenges may have been so substantial as to prevent any attempt at treatment. Nevertheless, the ability to achieve survivals comparable to those achieved in the "best" patient populations, i.e. those enrolled on clinical trials, is an important finding with implications for the delivery of cancer care across a broad spectrum of the US population.

Studies have shown that the ability to undergo treatment is negatively impacted not just by non–disease-related factors such as older age, ethnicity, lower socio-economic status, and

TABLE 2 Patient characteristics at diagnosis

Characteristic	Number, %
Age	
Mean (range), y	66 (48-83)
Median, y	64
≥ 70 years	8 (42.1)
Gender	
Male	12 (63)
Female	7 (37)
Histology	
Adenocarcinoma	19 (100)
Race	
White	11 (57.9)
African-American	3 (15.8)
Asian	3 (15.8)
Hispanic	2 (10.5)
Comorbidities	
Hypertension	13 (68.4)
Diabetes mellitus	8 (42.1)
History of previous cancer	5 (26.3)
Coronary artery disease/atherosclerosis	6 (31.6)
Alcohol abuse[a]	6 (31.6)
Smoker[b]	16 (84.2)
Lung disease (emphysema, COPD, asthma)	5 (26.3)
Prevalence of comorbidities	
1 comorbidity	1 (5.3)
2 comorbidities	2 (10.5)
≥ 3 comorbidities	16 (84.2)
ECOG performance status	
0	3 (15.8)
1	11 (57.9)
2	5 (26.3)
Insurance coverage	
Medicaid and Medicaid HMO	5 (26.3)
Medicare and Medicare HMO	9 (47.4)
Commercial	5 (26.3)

Abbreviations: COPD, chronic obstructive pulmonary disease; HMO, health maintenance organization.
[a] Defined as alcohol-related legal problems; drinking leading to physical injury; alcohol-related relationship problems; failure to fulfill major responsibilities at work, school, or home; [b] Defined as at least 10 pack-years.

limited education, but also by Medicare and Medicaid insurances[4-6], and lack of health insurance.[7] There is some suggestion in the literature that the environment in which care is delivered may have an impact on outcome,[8] and the question arises as to whether treatment environment can overcome the aforementioned barriers. In fact, it is known that patients with cancer from minority groups have a higher mortality compared with their white counterparts, but this is not the case when treatment is delivered at NCI-designated cancer centers[8], suggesting that place of service might influence cancer outcome.

Adequate insurance is crucial for cancer screening and for timely access to medical care. Members of ethnic minority groups are more likely to be uninsured or to have Medicaid insurance than non-Hispanic white people, both in the overall US population and in the population of individuals diagnosed with cancer.[7,21] About half of our patients had Medicare and Medicare-HMO coverage and a quarter had Medicaid or Medicaid-HMO insurance coverage, the latter a much higher proportion than the 4% in the 1998-2004 National Cancer Database.[21] Only one quarter had commercial insurance coverage, compared with the 57% in a published cost analysis of pancreatic carcinoma treatment[20] or to the 35.6% in the 1998-2004 National Cancer Database.[21] It is not particularly surprising that insurance status may be related to trial enrollment, the ability to deliver the best available standard of care, and outcome. It has been shown that uninsured patients have significantly lower adjusted odds of receiving cancer-directed surgery.[29] Uninsured or underinsured status also correlates with lack of social support which creates challenges for an appropriate and effective cancer treatment with overwhelming personal responsibilities, inflexible job schedules, lack of transportation, language barriers and cultural differences related to the perception of their illnesses and the recommended care.[30,31]

It previously has been shown that minorities are underrepresented in clinical trials[30,31] and have poorer outcomes, including for pancreatic cancer.[32] The percentage of minority patients in our population is much higher than the one observed in the 1998-2004 National Cancer Database (42.1% vs. 16.1%, respectively).[21] When compared with minority proportions identified in a population-based study in California with patients with adenocarcinoma of the pancreas[32] our population had a higher percentage of African-American and Asian patients, and a similar percentage of Hispanic patients (7.9%, 8.2%, 10.8% vs. 15.8%, 15.8, 10.5%, respectively). Barriers to clinical trial participation encountered by minority groups have been identified, and include, but are not limited to, lack of access to care, mistrust of research, logistical and financial challenges associated with traveling to cancer centers, and the definition of study entry requirements.[33] African-Americans received less CT (OR, 0.61) and Hispanics received less RT (OR, 0.5) after adjustment for age, stage, size of tumor, and insurance status in a multivariate regression model.[29] However, no significant differences in mortality by

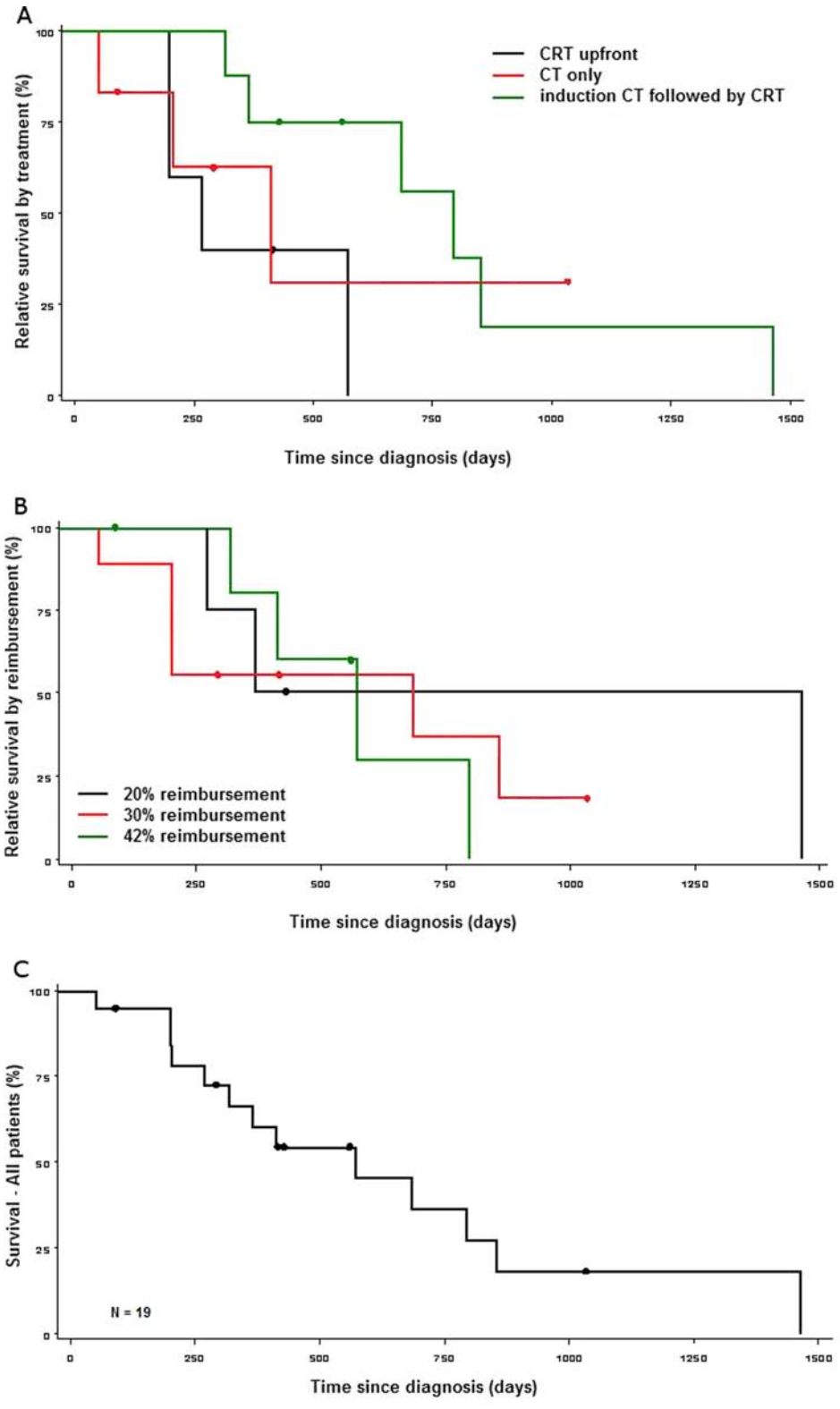

FIGURE 2 Kaplan-Meier survival curves. Panel A, different treatment modalities; Panel B, different levels of reimbursement for charges; Panel C, the whole cohort.

race was noted among those who attended NCI-designated cancer centers, suggesting that place of service might explain some of the cancer mortality excess observed in minority populations.[8]

It may be difficult to tease out the individual contributions of comorbidities, older age, and insurance coverage on outcome. Minority populations and those from lower socioeconomic strata have higher incidence of comorbidities and, as a consequence, less opportunity to be enrolled in a clinical trial or to obtain standard-of-care. The level and severity of comorbidities is described as lowest among patients with private insurance, higher for those who are uninsured or insured by Medicaid, and highest for those insured by Medicare.[34] In a multivariate analysis, patients with 3 or more comorbidities had approximately 40%-50% higher risk of death at 1-year.[34] Similarly, elderly patients (more than 40% of our patients were age 70 or older) are also underrepresented in clinical trials, exclusion criteria frequently limiting their enrollment. This observation is likely due to a higher level of comorbidities but also to the concern that they would be less likely to tolerate or benefit from the experimental treatment.[35]

Currently, induction CT followed by CRT is accepted as a best standard-of-care for LAPC, as it appears to select for patients without metastatic disease.[22-28,36-40] Our patients required intensive social support services to embark on, and complete, such treatment. The toxicities imposed by a CRT regimen did not prevent its administration, and in our series only one patient could not tolerate this approach. Despite multiple socio-economic limitations, our patients with LAPC achieved survivals comparable

with historical controls. Our results are representative of a wider urban community-based population, often not eligible for clinical trials. They reflect more accurately the complex inter-influences that multiple conditions exert on tolerance to and success rate of a treatment. Due to the very diverse population routinely served by Maimonides Cancer Center, investments aimed at reduction of disparities in care had been undertaken, at multiple levels. As part of such an initiative, widely and readily available interpreter services, physicians and nurses from diverse cultural backgrounds paralleling our community population, psychiatrists and psychologists, outreach programs, and intense and multicultural social services have been incorporated in the daily routine of our center. If these results are to be duplicated in other communities during these economically difficult times, the importance of these supportive services must be taken into account when setting overall health care budgets.

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