ORIGINAL ARTICLE

Variations in Medical Oncology Utilization for Pancreatic Cancer Patients in Nova Scotia

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ABSTRACT

Introduction Population studies have shown that only the minority of pancreatic cancer patients receive cancer directed therapy. **Methods** Primary aim of this study was to evaluate the referral rate for systemic chemotherapy, as a proxy for the quality of health care delivered to patients with pancreatic cancer in the province of Nova Scotia (Canada). The study population included a cohort of all patients older than 18 years of age who had the diagnosis of PC over a ten year period (April 1, 2001-March 31, 2011). Diagnostic codes of the International Classification of Disease for Oncology, 3rd edition were used to select patients with pancreatic cancer from the Nova Scotia Cancer Registry. Univariate and multivariate analyses were used to assess characteristics associated with the likelihood of receiving cancer directed therapy in the form of adjuvant or palliative chemotherapy. **Results** A total of 1,161 patients were included with mean age of 72 years. Elixhauser comorbdity score >1 was present in 41% of the cohort with 31% of patients living in rural areas and 40% belonging to low income groups. Surgical therapy was performed in 11.7%. Among patients who underwent resection, 60% were referred to medical oncologists for adjuvant chemotherapy *vs.* 36% for patients who were not surgical candidates (P<0.0001). Medical oncology consultations were completed only in 46% of patients who underwent surgical therapy *vs.* 31% of patients who were not surgical candidates (P<0.0001). Multivariate analysis of factors associated with referral to medical oncology services were younger age and low comorbidity status. **Conclusions** In Nova Scotia, cancer directed therapy in the form of surgery or chemotherapy for PC is offered only to a minority of patients. Rates of cancer directed therapy may reflect appropriate considerations of patients' preferences and functional status, however, other factors, including physicians' attitudes, may play a significant role.

INTRODUCTION

Pancreatic adenocarcinoma (PC) represents the fourth leading cause of cancer-related deaths in Canada [1]. The vast majority of patients are incurable at the time of diagnosis [2] and palliative chemo or chemoradiation therapy remain their only treatment options [3]. There is growing evidence that a significant proportion of PC patients do not receive chemotherapy, either for adjuvant purpose or for palliation [4, 5, 6, 7]. As a result, PC has the lowest rates of cancer-directed therapy out of all solid tumors [8]. This represents a modifiable factor that contributes to the poor prognosis of these patients [9].

In Canada, there continues to be a paucity of studies on factors that might be responsible for the low rate of cancer-directed therapy for PC patients [10, 11]. Therefore, primary aim of this study was to assess the management of pancreatic adenocarcinoma in Nova Scotia and the proportion of patients with PC who were referred to medical oncology specialists. Secondary outcomes were to assess if there was an increasing utilization of medical oncology resources over time and to explore if there were clinical and socio-demographic factors associated with medical oncology consultations.

METHODS

Patients Selection

The study population included a cohort of all patients older than 18 years of age who had the diagnosis of primary pancreatic cancers (PC) in the province of Nova Scotia, Canada over a ten-year period (April 1, 2001-March 31, 2011). Diagnostic codes of the International Classification of Disease for Oncology, 3rd edition (ICD-O-3) were used to select patients with PC from NSCR, a prospectively maintained database of all patients affected by malignant diseases in Nova Scotia and required by provincial law. Diagnostic codes of malignancies of the exocrine pancreas used for this study are summarized in **Table 1**. Each patient who satisfied the inclusion criteria was assigned an identification (ID) number to protect patients' privacy.

Additional administrative datasets were linked to the NSCR for completion of socio-demographic and clinical data as represented in **Figure 1**. Linked datasets included the Oncology Patient Information System (OPIS), Medical Service Insurance (MSI) Physician Services, Medical Service Insurance (MSI) Patient Registry, and the Canadian Institutes of Health Information (CIHI) Discharge Abstract Database (DAD) [12]. These datasets were linked to the NSCR by the Population Health Research Unit (PHRU) at Dalhousie University. The methodology used to link these administrative datasets has been described in details in previous manuscripts published by our group.

Data on medical and radiation oncology referrals and consultations were captured using OPIS registry in the interval of time between 3 months prior to and 6 months after the date of diagnosis. Similarly, surgical referrals were captured using MSI billing codes for consultation with a surgeon within 3 months prior to diagnosis and 6 months after diagnosis. Comorbidity index for administrative databases developed by Elixhauser *et al.* was used to identify patients affected by comorbidities in addition to PC [13]. Median geographical census income data obtained from Canadian Statistics [14, 15] were used as a marker for patients' socioeconomic status, with incomes divided into quintiles for statistical analysis.

The study protocol (CDHA-RS/2012-206) was approved by all the ethic review boards at each health district where patients received their treatment in the province of Nova Scotia and the investigators ensured adherence to confidentiality and safe storage of patients' information.

STATISTICAL ANALYSIS

Variables analysed in this study included sociodemographic, clinical, oncologic and administrative characteristics. Sociodemographic variables were patients' age and sex while clinical characteristics were patients' comorbidity score, rate of referral to surgical specialists and rate of surgical interventions, rate of medical and radiation oncology consultations and percentage of patients who received cancer directed therapy. Tumor data included anatomical stage and location of the neoplasms in the pancreatic gland. Finally, administrative characteristics included variables such as zip codes of patients' primary addresses that were used as proxies for median census income as published in previous studies and to stratify patients in groups living in rural versus urban areas. Distance to travel to tertiary medical centers were also calculated by using administrative data.

Continuous variables were expressed by median and inter-quartile range, and normality of data were checked

Table 1. Summary of all the International Statistical Classification of Diseases and Related Health Problems (ICD) codes used to identify patients with pancreatic adenocarcinoma included in this study.

ICD Codes Used for Identification of Location of Pancreatic Tumors	ICD-9-CM	ICD-10-CM
Malignant neoplasm of head of pancreas	157	C25.0
Malignant neoplasm of the body of pancreas	157.1	C25.1
Malignant neoplasm of the tail of pancreas	157.2	C25.2
Malignant neoplasm of the pancreatic duct	157.3	C25.3
Malignant neoplasm of other specified sites of pancreas	157.8	C25.7
Malignant neoplasm of pancreas part unspecified	157.9	C25.9
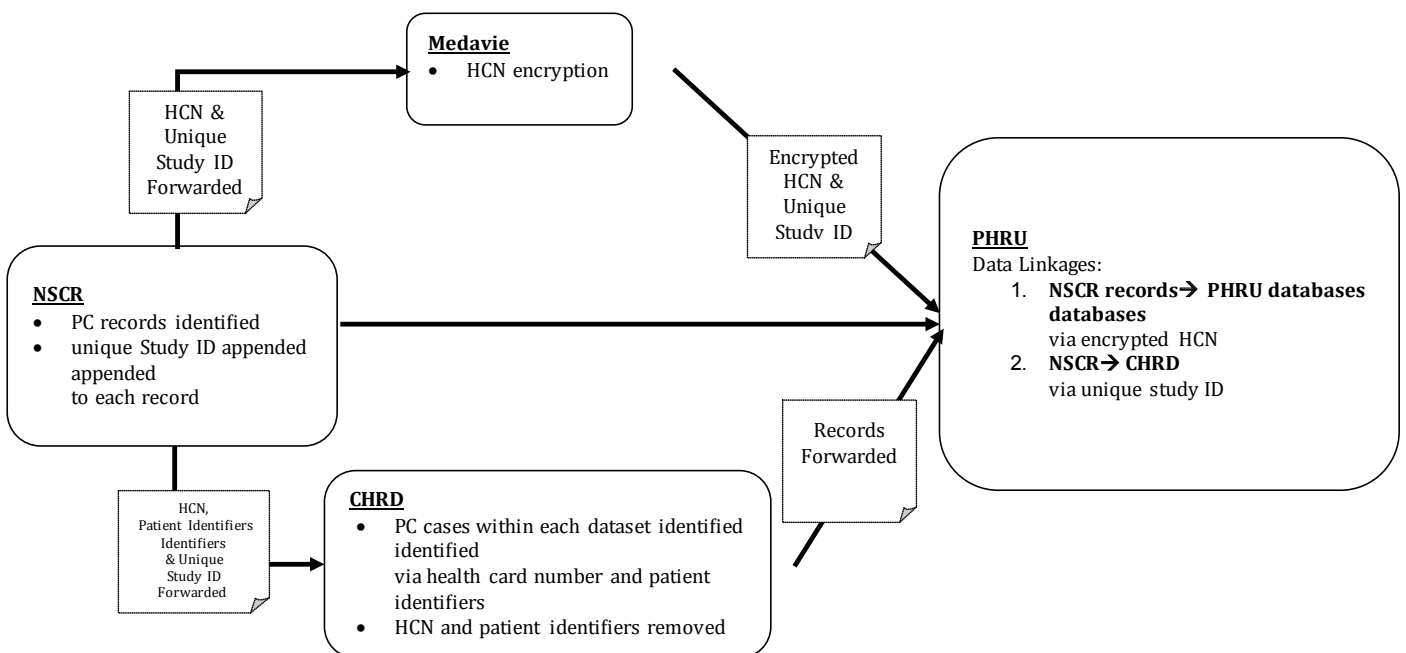
Figure 1. Schematic representation on how all the administrative database linkage was obtained to identify all the individuals affected by pancreatic cancer in Nova Scotia during the period between January 1, 2001 and December 31, 2011. **Legend:** NSCR (Nova Scotia Cancer Registry), HCN (Health Care Number), CHRD (Capital Health Radiology Department), PHRU (Population Health Research Unit, Dalhousie University).

using the Shapiro-Wilks test. Categorical variables were examined using Fisher's exact test when appropriate or Pearson chi square test and reported as proportion or percentages. Multivariate logistic regression analysis by maximum likelihood estimation was used to test the null hypothesis where referral to medical oncology was the dependent variable and age, gender, sociodemographic characteristics, number of comorbidities, surgical resection were potential predictors. A second logistic analysis was performed to evaluate predictors of consultations by medical oncologists after patients' referral. For logistic regression analysis, covariates were selected based on clinical relevance and from previous scientific literature and included if their p value was <0.20. If meaningful interactions between variables were identified, they were incorporated into the final models. Statistical significance of continuous and categorical variables, after checking for collinearity and adjusting for confounders and effect modifiers produced the final model.

All statistical analysis was carried out using SAS® (Version 8.2, Cary, North Carolina). Two-tailed analyses were performed unless otherwise specified and all statistical analyses were considered significant for P≤0.05.

RESULTS

Socio-demographic characteristics of the study population are summarized in **Table 2**. A total of 1,161 patients, with mean age of 72 years and equal distribution between males and females, satisfied the inclusion criteria. Patients living in rural areas and with low income represented 31% and 40% of the sample respectively. The head of the pancreas was the most frequent anatomical location (45%) of PC, and distant metastases were present in 50% of patients at the time of diagnosis. Surgical therapy with curative intent was performed on 136 patients (11.7%) while the rest of the cohort received best supportive therapy or palliative chemotherapy. Medical oncology referrals were requested for 39.5% of patients included in this study and consultations were documented in 33.6% of the entire cohort. When stratified by treatment modality, 60% of patients who underwent surgical resection were referred to medical oncologists in comparison to 36.2% of patients who did not undergo surgery (P<0.001) **Figure 2** and medical oncology consults were completed in 46% of surgical patients *vs.* 31% of non-surgical patients (P<0.001). No significant changes in the frequency of medical oncology referrals or consultations were observed over the study period **Figure 3**. At univariate analysis, factors that were associated with a higher likelihood of patients being referred to medical oncologists were younger age, low comorbidity score, higher income quintile, living in an urban area and surgical therapy for PC **Table 3**. When adjusted for age, sex, comorbidity score and place of residence, the only significant factors associated with the likelihood of referral to or consultation with a medical oncologist were younger age and a low co-morbidity score **Tables 4,5**.
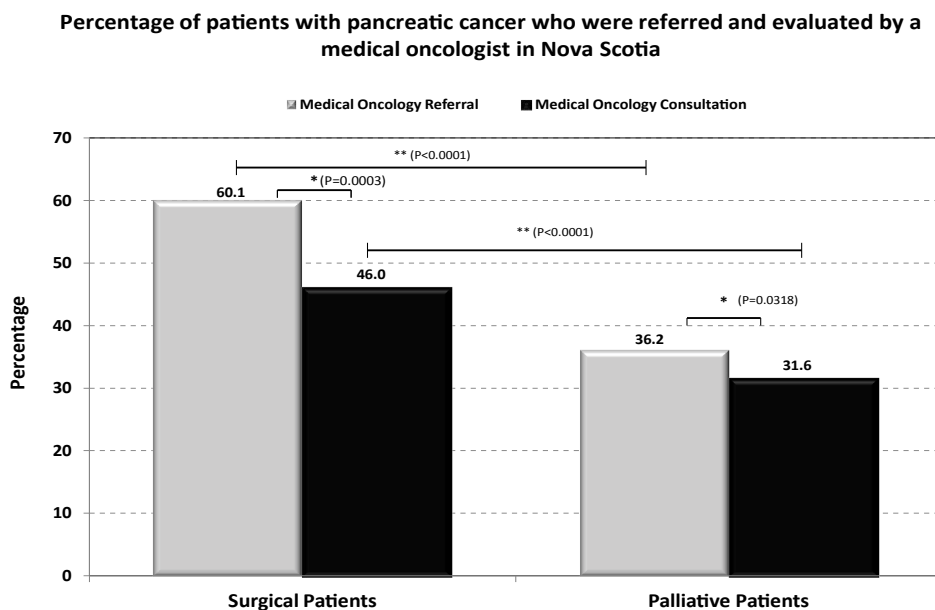
DISCUSSION

For patients with PC, the survival benefit of chemotherapy remains in the order of just a few months [2, 15]. Nevertheless, patients who receive chemotherapy enjoy better quality of life in comparison to best supportive therapy [2, 3, 4, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32]. Ideally, every patient with PC should be assessed and educated on the risks and the benefits of chemo or radiation therapies and ongoing clinical trials [33]. For most of other solid tumors, this is done in the settings of outpatient medical and radiation oncology clinics where patients can be actively engaged in important decisions regarding their treatments [34, 35, 36, 37]. However, this is not always the case and PC patients continue to have one of the lowest rates of cancer directed therapies among all patients with gastrointestinal tumors. Our study confirmed these findings as referrals to medical oncology in Nova Scotia were offered only to 39% of patients diagnosed with PC, and despite the growing evidence of the benefits provided by chemotherapy [38, 39], medical oncology referral rates did not increase over time.

For some patients, the decision not to be referred might have been due to their advanced age, comorbidities, and frailty or personal preferences. On the other hand, we cannot exclude that there might have been some

Table 2. Demographic and clinical characteristics of the study population.

Variable	Total Number of Patients (n=1,161)
Age, years, mean (SD)	72.5 (11.9)
Gender, n, (%)	
Male	572 (49.3)
Female	589 (50.7)
Elixhauser Comorbidity Index	
0-1	679 (58.5)
1	244 (21.0)
≥ 2	238 (20.5)
Residence Status, n, (%)	
Urban	608 (52.3)
Rural	367 (31.6)
Unknown	186 (16.0)
Income Quintile, n, (%)	
Q1 (Low)	280 (24.1)
Q2	196 (16.8)
Q3	197 (16.9)
Q4	200 (17.2)
Q5 (High)	193 (16.6)
Unknown	95 (8.1)
Treatment	
Surgical Therapy, n, (%)	136 (11.7)
Palliative Therapy, n, (%)	933 (80.3)
Unknown	92 (7.9)
Tumor Location, n, (%)	
Head	526 (45.3)
Body or tail	189 (16.2)
Other	446 (38.4)
Tumor Staging	
In Situ	5 (0.4)
Localized	117 (10.0)
Regional	157 (13.5)
Distant site(s)/node(s) involved	590 (50.8)
Unknown	292 (25.1)

Percentage of patients with pancreatic cancer who were referred and evaluated by a medical oncologist in Nova Scotia

Figure 2. Histogram representing the percentage of patients who were referred to a medical oncologist and the percentage of patients who had a consultation with a medical oncology specialist. There were significant differences in the proportion of referrals and consultations between the patients who had surgical interventions and patients who were palliated. In both groups, attrition between referral and consultation was significant as 24% of patients who had surgery and who were referred for adjuvant chemotherapy did not have a medical oncology consultation. Similarly, 14% of patients who were referred for palliative chemotherapy did not have a consultation with a medical oncologist.
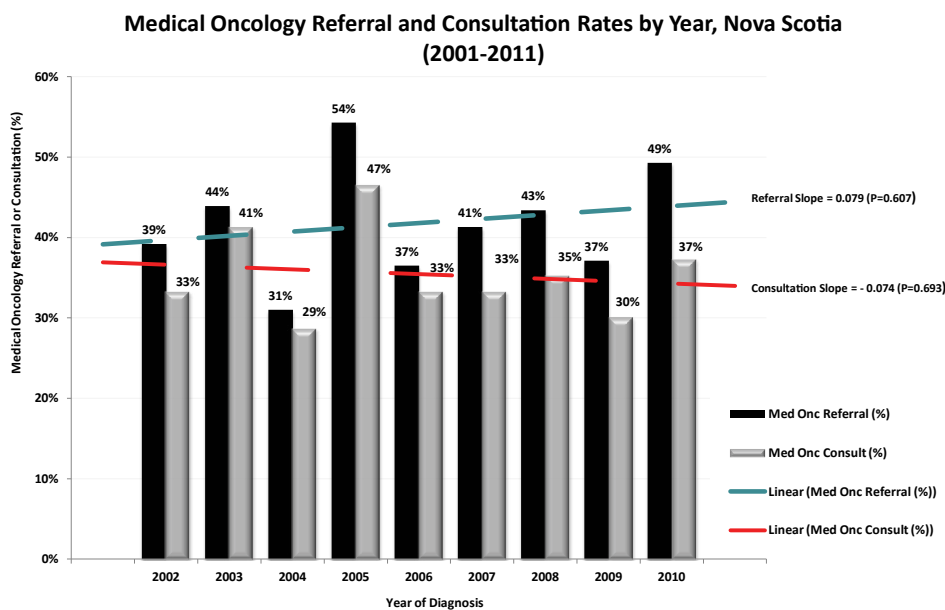
Figure 3. Graphical representation of the proportion of patients who were referred to a medical oncologist for consultation for adjuvant or palliative chemotherapy for pancreatic cancer in Nova Scotia during the period of nine years (2002-2010). No significant changes were identified in the trend of medical oncology referrals and consultations.

inconsistencies in how physicians managed these patients as fewer patients were referred if they did not undergo surgery [7]. The low rate of referral for chemotherapy in PC is not a new finding [5]. Some of the barriers that prevent PC patients to receive cancer-directed therapy may be due to the perception that surgery or chemotherapy medications are not sufficiently effective to justify their side effects or the costs associated with their use [40]. Our data would suggest that this perception might be stronger among medical specialists than surgeons. Unfortunately we were not able to explore this further as important clinical variables such as nutritional parameters, frailty scores and patients' preferences were not captured in administrative datasets.

There are several limitations of this study that must be acknowledged. In our opinion the most important is the retrospective design. Other shortcomings are the use of administrative databases and the fact that we enrolled only patients living in Nova Scotia where the effects of aging population, physicians shortages and reduced per-capita resources dedicated to health-care might have had a considerable effect on patients' management. Another limitation was the lack of histological confirmation of the diagnosis of PC for most of the patients who did not undergo surgery.

Our findings are comparable to several other population studies from the USA and Europe [5, 40, 41,

Table 3. Summary of univariate analysis of socio-demographic and clinical characteristics of patients with pancreatic cancer (PC) in relationship to referral and consultation with medical oncology specialists.

Variable	Referred to Medical Oncology	Non Referred to Medical Oncology	P Value	Visit to Medical Oncology	No Visit to Medical Oncology	P Value
Total Number, (%)	459 (39.5)	702 (60.4%)		368 (31.7)	702 (60.4)	
Mean Age, years, (SD)	67.8 (15.8)	77.2 (15.5)	**<0.0001**	66 (16.0)	75.8 (15.3)	**<0.0001**
Gender (%)						
Male	244 (53.1)	328 (46.7)	0.139	190 (51.6)	336 (47.8)	0.232
Female	215 (46.8)	374 (53.2)		178 (48.3)	366 (52.1)	
Comorbidity Score, n, (%)						
0	265 (57.7)	352 (50.1)		226 (61.4)	392 (55.8)	
1	100 (21.7)	129 (18.3)	**0.0018**	88 (23.9)	141 (20.1)	**0.0013**
≥2	67 (14.5)	156 (22.2)		54 (14.6)	169 (24.1)	
Unknown	27 (5.8)	65 (9.2)		0	0	
Income, n, (%)						
Quintile 1 (Low)	107 (23.3)	173 (24.6)		95 (25.8)	185 (26.3)	
Quintile 2	69 (15.0)	127 (18.0)		53 (14.4)	143 (20.3)	
Quintile 3	85 (18.5)	112 (15.9)	**0.0002**	75 (20.3)	122 (17.3)	**0.001**
Quintile 4	65 (14.1)	135 (19.2)		56 (15.2)	144 (20.5)	
Quintile 5 (High)	103 (22.4)	90 (12.8)		86 (23.3)	107 (15.2)	
Unknown	30 (6.5)	65 (9.2)		3 (0.8)	1 (0.1)	
Residence, n, (%)						
Urban	272 (59.2)	336 (47.8)		235 (63.8)	373 (53.1)	
Rural	130 (28.3)	237 (33.7)	**0.0035**	106 (28.8)	261 (37.1)	**0.003**
Unknown	57 (12.4)	129 (18.8)		27 (7.3)	68 (9.6)	

Table 4. Multivariate analysis for predictors of referrals to medical oncologists for patients with pancreatic cancer living in Nova Scotia.

Variable	All Patients (n. 1,161)*		Surgical Patients (n. 136) §		Palliative Patients (n. 933)**	
	Odd Ratio (95% CI)	P Value	Odd Ratio (95% CI)	P Value	Odd Ratio (95% CI)	P Value
Age	0.932 (0.921-0.944)	**<0.0001**	0.924 (0.878-0.973)	**0.0026**	0.938 (0.925-0.950)	**<0.0001**
Comorbidity Score						
0	**reference**		**reference**		**reference**	
1	1.121 (0.797-1.578)	0.5117	1.376 (0.438-4.323)	0.5852	1.119 (0.778-1.608)	0.545
≥ 2	0.665 (0.463-0.955)	**0.0273**	1.697 (0.478-6.029)	0.4134	0.590 (0.398-0.874)	**0.0086**
Residence						
Rural	**reference**		**reference**		**reference**	
Urban	1.335 (0.972-1.834)	0.0714	2.99 (1.01-8.86)	0.039	1.152 0.822-1.615	0.411

*   At multivariate analysis, sex (p=0.86) and income quintile (p=0.09) were no longer significant for all patients.

§   At multivariate analysis, sex (p=0.84) and income quintile (p=0.09) were no longer significant for surgical patients.

**   At multivariate analysis, sex (p=0.66) and income quintile (p=0.09) were no longer significant for palliative patients.

42, 43, 44]. On the other hand, outcomes of patients with PC in Canada are heterogeneous [45] and the results of our study might not be generalizable to other Canadian provinces. During the ten-year period analyzed, most of the patients with PC in Nova Scotia were treated with 5-Fluorouracil as Gemcitabine was only approved in the province in 2010. It is possible that the late approval of Gemcitabine might have had an effect on how medical oncologists perceived the benefits of systemic therapy and their likelihood of recommending it but we think that it was less likely to have a significant negative effect on referral rates.

This study has several strengths as it investigated a large population of PC patients in a Canadian province where, ideally, patients' socio-economic status should not have prevented access to health care as it is equally accessible to all Canadian citizens. In addition, this is the first population-based study on the utilization of medical oncology services for patients with PC in Nova Scotia and it is one of the few carried out in Canada.

Several conclusions could be drawn from our data. The first is that cancer directed therapy for PC continues to be offered only to a minority of patients. Therefore, more integrated multidisciplinary models of cancer care should be implemented since 5-year survival of PC patients in Nova Scotia remains one of the lowest in Canada [45].

The second is that the proportion of patients who were diagnosed with resectable disease remained below the

Table 5. Multivariate analysis for predictors of consultations with medical oncologists for patients with pancreatic cancer living in Nova Scotia.

Variable	All Patients (n. 1,161)*		Surgical Patients (n. 136)		Palliative Patients (n. 933)**	
	Odd Ratio (95% CI)	P Value	Odd Ratio (95% CI)	P Value	Odd Ratio (95% CI)	P Value
Age	0.927 (0.915-0.939)	**<0.0001**	0.905 (0.860-0.951)	**<0.001**	0.930 (0.917-0.943)	**<0.001**
Comorbidity Score						
0	**reference**		**reference**		**reference**	
1	1.186 (0.833-1.688)	0.343	1.205 (0.415-3.497)	0.732	1.187 (0.814-1.730)	0.373
≥ 2	0.634 (0.430-0.934)	**0.021**	1.151 (0.378-3.507)	0.805	0.580 (0.381-0.883)	**0.011**
Residence						
Rural	**reference**		**reference**		**reference**	
Urban	1.464 (1.049-2.044)	0.0252	2.343 (0.808-6.798)	0.1171	1.348 (0.944-1.925)	0.099

*   At multivariate analysis, sex (p=0.80) and income quintile (p=0.18) were no longer significant for all patients.

§   At multivariate analysis, sex (p=0.75) and income quintile (p=0.82) were no longer significant for surgical patients.

**   At multivariate analysis, sex (p=0.69) and income quintile (p=0.08) were no longer significant for palliative patients.

desirable level reported in other centers where surgery is performed in up to 20-25% of patients [44]. The last point is that a significant proportion of patients were not referred to medical oncologists for chemotherapy due to their age or comorbidities. This was more common for patients living in non-urban locations, with lower socio-economic status and who did not undergo surgical therapy. Although lower rates of cancer-directed therapy in some groups of patients may reflect personal preferences or a low functional status, the extent of variations seen in this study would suggest that physicians' attitudes may have played an important role.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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