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Original Article

Resource Use and Costs Associated to the Initial Phase of Treatment for Patients with Colorectal Cancer Receiving Post-Surgery Chemotherapy: A Cost Analysis from a Healthcare Perspective

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Abstract

Background: To estimate the resource use and costs associated to the initial phase of treatment for colorectal cancer in Iran.

Methods: A retrospective study was conducted using routinely collected data within Electronic Health Records System (SEPAS), a national database representing public hospitals in Iran between March 20, 2016 and March 19, 2017. Primary end points included healthcare resource use, direct medical and non-medical costs of care in the 12-month study period.

Results: The study population included 657 patients with colorectal cancer who underwent surgery and the follow-up chemotherapy. We estimated a total direct cost of $21,407 per patient. The results indicated that direct medical costs were primarily driven by inpatient hospital care, followed by surgery, chemotherapy, and diagnostic services.

Conclusion: The initial 12-month of treatment for colorectal cancer, including surgery and the follow-up chemotherapy, is resource intensive. The total direct costs associated to the disease are remarkable, with Inpatient hospital services being the main contributor followed by surgery and chemotherapy.

Keywords: Colorectal cancer; Costs; Direct medical costs; Resource use

Introduction

Colorectal cancer is the second most commonly diagnosed cancer among females and the third in males with nearly 1.8 million new cases worldwide in 2018 (1). According to the most recent data from WHO, the disease is ranked second in terms of mortality with approximately 881,000 deaths estimated in 2018 (1, 2). The epidemiologic burden of the disease is geographically heterogeneous, with its regional incidence varying over 10-fold. It is determined to be common in both industrialized

and developing countries (3-5), with South Asia having the highest number of new cases (6). In Iran, colorectal cancer is the fourth most common cancer with an incidence rate of 12.9% in 2018 (2, 7). It is accounting for 8.4% of all cancer types in the country (8). Substantial economic burden of the disease is established in a study reporting a disability adjusted life year (DALY) of 52.53 yr for colorectal cancer patients in Iran (9). The average cost of treatment was found to be $10715, $15920, $16452, and $16723 among patients diagnosed with disease stage I to IV in a study based in Isfahan city (10).

Evaluation research on the rapidly increasing costs associated with cancer care is becoming more critical as the emerging use of novel treatments including targeted therapies highlights a major financial burden to patients and their families. As treatment options expand, highly expensive agents become available in oncology practice where combination therapies and multiple lines of treatment are being used more frequently. A strong body of evidence shows that the average cost of cancer has increased dramatically over the past decades mainly due to the newly developed treatments (11-16). According to a US-based study, the cost of bevacizumab for the treatment of colorectal cancer is estimated to be up to $9,000 per month (17,18).

We conducted a cost of illness study to investigate resource use and costs associated to colorectal cancer in Iran.

Materials and Methods

A retrospective study was conducted using data on 657 patients identified through Electronic Health Records System (SEPAS) between March 20, 2016 and March 19, 2017. SEPAS is a national database that offers a diverse representation of public hospitals affiliated to the Ministry of Health and Medical Education (MOHME) in Iran. Patients were selected from the five regions of the country defined as administrative regions by Ministry of Interior in 2014 (Fig. 1 represents how provinces are distributed across the regions). All patients who met the eligibility criteria and received treatment during the 12-month study period were included in the analysis, and thus no sampling was required. Eligible patients were aged ≥18 yr, with a colorectal cancer diagnosis (ICD-10-CM code C18.9) who were received the initial phase of treatment including surgery and the follow-up chemotherapy in the first-year post diagnosis. Subjects treated with concomitant radiotherapy were also eligible. Continues coverage with at least one claim for surgery and one for chemotherapy within the 12-month study period was required for inclusion. Patients with inoperable disease, noncompliance with treatment phase (surgery followed by chemotherapy), life-expectancy of less than six months and incomplete claims were excluded from this study. Index date was defined as the first surgery date, and the episode window was from the index date to the last chemotherapy or chemoradiation visit over the observation period.

Outcome Measures

This study was conducted from a healthcare perspective. The primary endpoint was total costs associated to the initial phase of treatment over the 12-month observation period. This includes both direct medical and non-medical costs. Hoteling and guardian services during the hospital stays were defined as direct non-medical costs. Data on lost productive years of life due to disease, as well as other related costs falling on sectors outside healthcare were not available in the source database. In the base-case analysis, a PPP conversion factor was used to convert all the cost to the US Dollars with USD= 8,212.15 Iranian Rial [IR] in 2016 (>80% of the data occurred in 2016) as it seems to be more stable than market exchange rate which is heavily impacted by other external factors such as economic sanctions (19). Hospital resource use and contacts to health care professionals were priced according to the tariffs defined for 2016-2017, the year of service delivery, as reflected in SEPAS database.

Statistical Analysis

The basic demographics were described in mean (with standard deviation) and median (with inter

quartile range (IQR)) for the 12-month study period. We used non-parametric tests where appropriate, as the cost data was not normally distributed. After log transformation of total costs, a fixed effect linear regression analysis was performed for the geographical regions of the providers to better understand the impact of explanatory variables including age, gender, health insurance plan, and source of admission (inpatient, outpatient and emergency department). Data were assumed to be missing at random, and the analyses carried out using available data. The cutoff for statistical significance was an alpha of 0.05. The analysis was performed in STATA 15.

Furthermore, a one-way sensitivity analysis was conducted to investigate how the costs estimates looked like if the official market exchange rate was used to convert the costs in to the US Dollars (USD). Despite the claim that most of the health services in Iran are heavily subsidized, there is lack of solid evidence suggesting that the payment schedules to highly specialize medical providers or otherwise expensive biopharmaceutical products are substantially below the competitive fee-schedules in the region or across the world. To say the least, the international versus domestic price gap is much narrower than that of other major households' consumption items such as gas and food staples. In contrary, the general sentiment is indicative of rather unbearable and in cases catastrophic treatment expenses for cancer patients and the families. External factors such as economic sanctions and informal payments to providers as well as the increasing role of black market might have inflated the treatment costs just enough to assess the impact of using official market exchange rate in the sensitivity analysis. Therefore, all costs were converted to USD based on the average market exchange rate in 2016 (USD= 31,389 IR) (20).

Results

Patient Characteristics

Overall, 657 inpatients with colorectal cancer received the initial phase of treatment, surgery and the follow-up chemotherapy between Mar 20, 2016 and Mar 19, 2017 were initially identified within SEPAS. After screening for cancer-related admissions, continuous enrollment, and post-surgery chemotherapy admission, we found 489 individuals to be eligible for the study. Patients who underwent surgery or received their first chemotherapy over the last two months of the study were excluded (n=22). Among the 467 patients included in the analysis, mean age at the time of first admission was 55.2 ± 13.5 yr (Median: 56 [IRQ: 46-64]). Patients were predominantly male (59.5%). The most frequent source of hospital admission was inpatient setting (96.5%), followed by emergency department (2.5%), and outpatient setting (1%). Social security organization (SSO) and Iran Health Insurance Organization were the main health insurance plans that almost equally covered 48.4% and 43.9% of the study population, respectively. There were 6 patients (1.3%) with no insurance coverage. Study sample was heterogeneously distributed across the five administrative regions of the country with 39% and 11.3% being included from regions 1 and 4, respectively.

Healthcare Resource Use

Of the total 2,482 hospital admissions during the observation period, 1975 (79.6%) were chemotherapy-related. Patients were hospitalized for a median of 23 (IQR 15-35) days. The inpatient resource use was mainly driven by physician visits followed by specialist consulting visits with median of 12 and 2 visits, respectively (Table 1).

Direct Healthcare Costs

Total direct costs associated with the initial phase of treatment varied substantially across the five regions in the county (Fig. 1).

Table 1: Healthcare Resource Use During the Episode of Care

Resource Use	*Patients (n)*	*Mean ($)*	*SD ($)*	*Min ($)*	*Max ($)*
Number of hospital admissions	467	5	4	1	21
Number of chemotherapy admissions	467	4	4	1	21
Number of specialist consulting visits	321	4	6	7	49
Number of physician visits	426	19	25	5	274

Fig. 1: Geographical distribution of average direct costs associated with the initial phase of treatment for colorectal cancer in Iran

Region 1 (Alborz, Golestan, Mazandaran, Qazvin, Qom, Semnan, and Tehran provinces with 23,343,033 million population); region 2 (Bushehr, Chaharmahal, Fars, Hormozgan, Isfahan, and Kohgiluyeh provinces with 12,973 million); Region 3 (Ardabil, East Azerbayjan, West Azerbayjan, Zanjan, Gilan, and Kordestan provines with 12,782,820 million); Region 4 (Hamedan, Ilam, Kermanshah, Khuzestan, Lurestan, Markazi provinces with 11,739,552 million); and Region 5 (Kerman, North Khorasan, South Khorasan, Khorasane Razavi, Sistan and yazd provinces with 13,145,227 million population). All costs are converted to the USD using PPP exchange rate (USD=8212.15IR).

Region 4 found to have the highest direct costs over the 1-year observation period with an average cost of $30,204 (95%CI: 16909-20394), followed by region 3 with $25,558 (95%CI: 21,556-29,559), region 2 with 22,072 (95%CI: 18,071-25,945), region 1 with 18,716 (95%CI: 16,909-20,394) and region 5 with 18,458 (95%CI: 16,264-20,652). Direct medical and non-medical costs accounted for 79% and 21% of the total direct costs, respectively.

The overall direct cost associated to the initial phase of treatment was $21,407 per patient, with medical services being the key contributor accounting for $17,017. The medical costs were mainly driven by inpatient hospital services

(42.6%), followed by surgery (23.2%), chemotherapy (16.5%), diagnosis (9%), and physician visits (8.4%). The cost associated with the chemotherapy agents was nearly four times greater than cost of medications used in the operation room (Table 2).

Table 2: Direct Costs Associated to the Medical and non-Medical Services in the Base-Case Analysis (USD= 8212.15 IR)

Direct Medical Costs	*Patients (n)*	*Mean ($)*	*SD ($)*	*Min ($)*	*Max ($)*	*Total costs ($)*	*Total costs per patient ($)*
Surgery-related Costs							
Surgery	467	665	832	32	7615	310605	665
Anesthesia	405	571	440	24	4182	231274	571
Surgeon	358	1536	1140	18	8158	550621	1538
Operation room drug	262	754	1807	11	12289	197336	754
Surgical assistant	203	226	212	0	2156	45856	226
Operation room resource Use	340	1498	1833	20	9255	509400	1498
Chemotherapy Costs	467	2814	2750	142	14069	1311284	2808
Radiotherapy Costs	5	2956	3356	382	6996	14768	2953
Inpatient Hospital Costs							
Inpatient drug	424	6712	9719	13	76285	2847541	6716
Nursing care	461	393	719	20	9100	181368	393
Inpatient resource use	357	996	1910	4	13424	355563	996
Diagnostic Costs							
Laboratory tests	454	652	1613	10	32011	296164	652
Pathology	234	739	5640	3	86494	86494	370
CT scan	178	299	195	52	1407	53210	299
Sonography	181	242	295	12	2982	43712	242
MRI	36	239	146	94	720	8570	239
ECG/EEG	309	116	181	11	1653	35632	116
Radiography	392	80	152	2	2646	31196	80
Nuclear medicine	19	401	232	38	974	7622	401
Other diagnostics tests	166	545	1665	0	16650	90502	545
Other diagnostic services	221	264	704	0	7732	58407	264
Rehabilitation Costs							
Physiotherapy	48	109	113	22	557	5234	109
Rehabilitation services	12	183	105	59	310	2196	183
Cost of Visits							
Physician visit	422	1329	1368	8	14456	560376	1328
Specialist consulting visit	317	354	383	6	3214	112186	354
Direct Non-Medical Costs							
Guardian services	89	288	300	2	1381	25693	288
Hoteling	449	4505	3188	103	29559	2024208	4508
Total Direct Medical Costs	467	17038	13037	809	89063	7946830	17017
Total Direct Non-Medical Costs	467	4388	3266	112	29559	2049901	4389
Total Direct Costs	467	21427	14973	1255	95000	9996731	21407

A fixed-effect linear regression analysis using limited explanatory variables such as patient demographics, payer type and admission source did not provide a satisfactory estimate for the total costs (Table 3). Similarly, none of the variables showed statistically significant association with the number of chemotherapy admissions during study period.

Table 3: Regression Model Estimates, Resource Use and Costs Drivers in Advanced Operable Colorectal Cancer

Parameter	***Chemotherapy Admissions***				***Total Direct Costs***			
	Estimate	Standard Error	t	*P*-value	Estimate	Standard Error	t	*P*-value
Intercept	8.07311	0.08377	96.37	0.00	4.61155	0.94813	4.86	0.00
Age	0.00035	0.00098	0.36	0.72	0.00118	0.01181	0.10	0.92
Gender	0.00799	0.02816	0.28	0.77	0.06185	0.34744	0.18	0.85
Insurance	-0.00925	0.01489	-0.62	0.53	-0.07807	0.14436	-0.54	0.58
Admission source	0.02999	0.04050	0.74	0.45	-0.37977	0.39504	-0.96	0.33

Sensitivity analysis

A one-way sensitivity analysis was performed to investigate how cost estimates would be affected if the official market exchange rate was used in converting the costs to the US Dollar. The costs significantly dropped by almost 74% when estimated using the market exchange rate (USD= 31,389 IR). Sensitivity analysis resulted in a mean total cost of 5,605 ± 3,918 in one year, almost three quarter less than the costs estimated in the base-case analysis using PPP factor (Table 4). Although, the costs need to be seen in an adjusted context where the patient's income and ability to pay is equally adjusted and converted to USD using the free market exchange rate.

Discussion

This study estimated the total direct costs associated to the treatment of colorectal cancer during the initial 12-month of care at public hospitals in Iran. Data from the current analysis, indicated that colorectal cancer causes significant burden with a mean direct cost of $21,427 ± 14,973 during the first year. The costs were dominated by inpatient hospital care and differed markedly across the geographical regions of the country. We studied the initial phase of treatment as it involves substantial resource use from pre-operation diagnosis to post-surgery chemotherapy. Studies previously conducted in Iran, Australia, and the United States along with other European-based analyses using data from Spain, Finland, Germany, and the United Kingdom have also demonstrated that the first-year treatment of the disease is resource intensive and the costs significantly increase by disease stage (21-24).

Our findings were comparable with the treatment cost associated to the primary stages of the disease across the Europe, ranging from €15,000 in Germany (cost year 2009) (25), to €22,200 in Denmark (26). In the US, the annual treatment costs reached approximately $28,000 for earlier stages of the disease and increased up to $46,000 in stage III (cost year 2014) (27). Compared to the current analysis, lower costs of treatment were found in a previously published study in Iran, where the costs ranged from $10,715 to $16,723 for disease stage I to IV (cost year 2012) (10). The study recruited patients from a single medical center in Isfahan city, located in region 2, for which we found a region-specific mean cost of $22,072 in the current analysis.

Table 4: Results of Sensitivity Analysis for Cost Estimates Using the Official Market Exchange Rate (USD=31,389 IR)

Direct Medical Costs	*Patients (n)*	*Mean ($)*	*SD ($)*	*Min ($)*	*Max ($)*	*Total costs ($)*	*Total costs per patient ($)*
Surgery-related Costs							
Surgery	467	174	217	1	1993	81262	174
Anesthesia	405	149	116	6	1094	60507	149
Surgeon	358	402	298	4	2134	144056	403
Operation room drug	262	197	473	0	3215	51628	197
Surgical assistant	203	59	55	0	564	11997	59
Operation room resource Use	340	392	479	0	2421	133272	392
Chemotherapy Costs	467	737	720	37	3681	343065	735
Radiotherapy Costs	5	774	878	100	1831	3864	773
Inpatient Hospital Costs							
Inpatient drug	424	1756	2543	3	19958	744988	1757
Nursing care	461	103	188	5	2381	47450	103
Inpatient resource use	357	261	500	1	3512	93025	261
Diagnostic Costs							
Laboratory tests	454	171	422	2	8375	77484	171
Pathology	234	193	1476	1	22629	22629	96
CT scan	178	78	51	14	368	13921	78
Sonography	181	64	77	3	780	11436	64
MRI	36	63	38	24	189	2242	63
ECG/EEG	309	30	48	3	432	9323	30
Radiography	392	21	39	0	692	8162	21
Nuclear medicine	19	105	60	10	254	1994	105
Other diagnostics tests	166	143	436	0	4357	23677	143
Other diagnostic services	221	69	184	0	2022	15281	69
Rehabilitation Costs							
Physiotherapy	48	29	30	6	145	1370	29
Rehabilitation services	12	48	28	16	81	575	48
Cost of Visits							
Physician visit	422	348	358	2	3782	146609	348
Specialist consulting visit	317	92	100	2	841	29350	92
Direct Non-Medical Costs							
Guardian services	89	75	78	1	361	6723	75
Hoteling	449	1179	834	27	7734	529583	1180
Total Direct Medical Costs	467	4457	3411	211	23301	2079165	4452
Total Direct Non-Medical Costs	467	1148	854	0	7734	536306	1148
Total Direct Costs	467	5605	3918	329	24855	2615471	5601

The higher costs associated to the treatment in our study relates to the episode of care being limited to operation and the follow-up chemotherapy during the first-year after cancer diagnosis. Moreover, we included direct non-medical costs of the disease including hoteling and caregiver costs during hospital stays. With respect to the estimated costs in our study though, it needs to be taken in to account that we could not associate the costs to any stage of the disease due to lack of clinical data in SEPAS.

In addition, the nature of the data limited our ability in addressing the current gap in the published literature regarding the costs associated to comorbid conditions in colorectal cancer. Significant contribution of comorbidities in total costs of treatment is demonstrated in Nordic countries (26).

According to a study, almost half of the colorectal cancer patients (45%-47%) were diagnosed at younger ages (<50 yr) in Iran (10), which is consistent with our findings. This would significantly impact the productive life years lost by disease. Only 29% of the lifetime financial cost of cancer was associated to the health system, with caregiver's burden and productivity loss being accountable for more than half of the total costs (24). Similarly, a burden of illness study conducted in Iran indicated that productivity lost due to premature mortality is a significant component (>60% contribution) in total costs of colorectal cancer (28). Nevertheless, lack of inclusive data on social cost components in SEPAS did not let us to investigate indirect costs. Further research is required to incorporate data on patient's risk profile as more inclusive data become available.

As far as inpatient care is concerned, our findings indicated that hospitalization accounted for almost half (42.6%) of the medical costs, followed by surgery (23.2%) and chemotherapy (16.5%). Consistent with our findings, medications are found to be the largest contributor in to the total costs (24, 26). With respect to the chemotherapy medications, a US-based study reported a significant contribution by 42% to the medical costs in a 6-month episode of care for colorectal cancer (27). Likewise, chemotherapy accounting for nearly half (50.4%) of the total costs of the disease was found in Iran (28). This is however, more than double the size of the contribution we found in our study for chemotherapy. The difference is most probably because; first, the treatment was limited to the initial 12 months from diagnosis in our analysis, with an average of only four post-operation chemotherapy admissions per patient. Second, cost of chemotherapy medications was estimated through interviewing specialists in Vahdatinejad's study. A differentiation by prescribed medications is needed to satisfy the requirements of such comparison in future research.

Our findings should be interpreted in the context of several important limitations. First, patients were recruited from public hospitals among those who survived at least one-year post treatment. This may have limited generalizability of our findings. Second, the episode of care was defined based on the treatments received including chemotherapy post-surgery. The possibility of misclassification of patients who experienced a gap in their treatment path might have led to selection bias. Although using administrative data has a great potential for studying cost of care in the context of healthcare reforms (29), the nature of data introduces potential sources of bias.

Conclusion

The initial 12-month of treatment for colorectal cancer, including surgery and the follow-up chemotherapy, is resource intensive. The total direct costs associated to the disease are remarkable, with Inpatient hospital services being the main contributor followed by surgery and chemotherapy. The results of the current analysis from a basis for future cost-of-illness studies, as well as economic evaluation of treatment scenarios.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission,

redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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