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 healthcare 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 into 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 household's 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     |

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    | 284754          | 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                        |
| Costs                                |              |          |        |         |          |                 |                             |
| 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 into 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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