Prescription of Cancer Treatment Modalities in Developing Countries: Results from a Multi-Centre Observational Study*

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Abstract

Background: Treatment is an important component of a comprehensive cancer control approach and its outcomes strongly depend on infrastructure, equipment, human and financial resources available. Therefore it is imperative to generate evidence-based tools to assist health policy makers from low resourced countries in planning efficient and equitable treatment services for a defined population based on what is feasible to these settings. Methods: The intended cancer specific treatment planned and written in the patients’ medical record (treatment prescription) of untreated adult cancer cases (≥18 years of age), excluding non-melanoma skin cancer, was recorded in a chronological way from 1 January 2012 onwards in a group of eight comprehensive cancer centres located in middle income countries and offering the main modalities of cancer treatment. 

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treatment (surgery, medical oncology and radiotherapy). 

**Results**: A total of 17,713 medical records were reviewed, of which 7106 (54.2%) met the eligibility criteria. Prescription of main cancer treatment modalities were distributed as follows: 57.6% for chemotherapy (n = 4093), 56.8% for surgery (n = 4038), and 46.8% for radiotherapy (n = 3327). There was a predominance of plans consisting of combined treatment modalities over monotherapy (55.2% versus 44.8%). At the time of diagnosis 54.3% of the cancer cases had disease that had spread beyond the primary site, 41.2% were considered as having local disease and in 4.5% of the cases the information on disease extension was unknown. 

**Conclusions**: The results obtained should be seen as an approximation of cancer treatment service demand based on what it is currently practiced and therefore feasible in developing countries, particularly in middle income countries.

**Keywords**

Cancer Treatment, Developing Countries, Health Services Needs and Demand, Resource Allocation, Observational Study

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**1. Introduction**

Cancer is expected to become an increasingly important proportion of the global burden of disease in the decades to come. According to the International Agency for Research on Cancer (IARC), there were 14.1 million estimated new cancer cases in 2012. These numbers are projected to rise to over 20 million every year by 2030 [1]. Today, about 60% of these new cases are from the developing world, and it is expected that by 2030 they will represent over 70% [2]. The current and foreseen cancer burden is challenging public health policy makers to implement comprehensive approaches in cancer control involving the different levels of care. This is particularly important in low resourced countries, where the cancer mortality to incidence ratios are significantly higher than in high income countries [1].

Based on the knowledge and technology available today, it is estimated that approximately 40% of cancer deaths could be avoided by preventive measures, early detection and effective treatment [3]. Access to effective therapies as well as the introduction and dissemination of a multidisciplinary clinical approach in cancer patients’ management have proved to have a predominant effect on survival increase and mortality reduction for some cancers [4]-[6]. However, limited infrastructure, equipment and insufficient number of trained human resources to cover the current patient load impede the capacity of many developing countries to improve treatment outcomes [7]. Therefore, it is imperative to generate evidence-based tools to assist countries in planning efficient and equitable treatment services for a defined population based on an estimation of demand versus resources available.

Currently, information on cancer treatment service demand in low resourced settings is very limited. The main modalities of cancer treatment are surgery, systemic therapies (chemotherapy, hormonal therapy and biological agents) and radiotherapy, which can be delivered alone or in combination and either with curative or palliative intent. The development of new and/or strengthening of operational services delivering these therapies is associated with increasingly high costs [8], therefore making realistic projections is critical to maximize infrastructure, equipment, financial and human resources at a population level. Considering radiotherapy, the information available has been generated mainly in developed countries; the estimates of service demand are based on expert’s opinion [9], rate of utilization [10]-[19], or on what should be prescribed according to clinical guidelines [18] [20] [21]. However, patterns of cancer incidence, stage at diagnosis and access to treatment in developing countries are distinct, thus indications for surgery, systemic therapies and radiotherapy may vary considerably.

The present study aims to provide information on the frequency of prescription of the main treatment modalities in new cancer patients from eight comprehensive cancer centres located in different developing countries. Cancer treatment prescription was considered as the intended cancer specific treatment planed and written in the patients’ medical record; recording treatment delivery, completeness and outcome is out of the scope of this study. It is expected that this information will provide an estimate of the cancer treatment prescription rates and therefore have applicability in planning and allocating resources in developing countries.
2. Methods

This observational study was designed and coordinated by the Programme of Action for Cancer Therapy (PACT) of the International Atomic Energy Agency (IAEA), the Coordination Unit, in Vienna and conducted in eight comprehensive cancer centres located in developing countries, classified as middle income countries by the World Bank according to their Gross National Income (GNI) per capita in 2012 [22] from Asia, Europe, Latin America and Middle East regions.

2.1. Criteria for Selection of Centres

The pre-selection of participating centres was done by the Coordination Unit through review of IAEA reports of cancer control assessment missions, known as imPACT reviews [23] [24], conducted from 2005 to 2012 in developing Member States and information shared by Member States representatives at regional meetings on cancer control organized by the IAEA, and by performing internet search to identify potential eligible centres.

The following criteria were used to identify potential participating centres: 1) have services for the main modalities of cancer treatment, namely surgery, medical oncology and radiotherapy; 2) be able to obtain data on cancer diagnosis and subsequent treatment modality/modalities prescribed in a chronological way from the hospital registry and/or medical records in 2012; 3) register on average 2000 or more new cancer patients every year; and 4) have over 50% of those patients initiating treatment at the centre.

Seventeen cancer centres were identified as potential candidates to be included in the study. To access eligibility, a brief questionnaire addressing the abovementioned criteria was sent to those centres; 16 responded and 10 met the criteria. Eligible centres were invited to an introductory technical meeting held in Vienna in April 2013 where cancer centres’ representatives confirmed availability of main cancer treatment services, existence of multidisciplinary teams for commonest cancer sites, and considered infrastructure, workforce, waiting time to commence treatment as adequate to the workload in 2012. Out-of-pocket expenditure was also reported as minimal or non-existent in all centres. At the meeting, the feasibility of conducting the study was assessed and the protocol and timeline were discussed and approved.

The following eight cancer centres complied with the requirements1 and timeline and were included in the study: Brazil National Cancer Institute, Cancer Institute of Iran, Hacettepe University Oncology Hospital (Turkey), Institute of Oncology “Prof. Dr. Ion Chiricuță” (Romania), King Hussein Cancer Centre (Jordan), National Institute of Neoplastic Diseases (Peru), National Institute of Oncology and Radiobiology (Cuba), and Tata Memorial Hospital (India).

2.2. Criteria for Selection of Cases

All patients that were registered in each participating cancer centre and were assigned with a medical record number in 2012 were recorded in a chronological way from 1 January 2012 onwards. From this pool of cases, the population to be analysed consisted of untreated adult cancer cases (≥18 years of age), excluding non-melanoma skin cancer, with an established treatment plan to be initiated in the cancer centre, or elsewhere.

Although all cancer centres in this study treat paediatric patients, those cases were excluded since the majority are referred to specialized haematological hospitals before establishing a treatment plan and the age limit of patients admitted in the different paediatric oncology departments varied from 14 to 18 years of age.

2.3. Data Collection and Analysis

A database was created using Microsoft Excel 2007 and distributed to each participating cancer centre, in which seven variables were recorded for every eligible case. These variables were: age [1]; gender [2]; cancer site [3]; most valid method of diagnosis [4]; extension of the disease [5]; treatment prescribed [6]; and, type of radiation therapy prescribed [7]. Cancer sites were coded according to the 10th edition of the International Classification of Diseases (ICD-10) [25]. Treatment modalities to be recorded were surgery, chemotherapy, radiotherapy, hormonal therapy, radio-iodine therapy and immunotherapy, alone or in combination.

1Requirements to participate in the study included confirmation of acceptance and nomination of an investigator by the Directors of participating cancer centres and submission and approval of the study protocol by respective institutional review boards.
The Coordination Unit received anonymous data submitted by the cancer centres between 1 June and 30 November 2013 (“reporting period”), and performed periodic data quality control. Inconsistencies and incompleteness of data were discussed in a group meeting held in Vienna in December 2013. Final data from centres’ databases were merged into one database and descriptive analyses were done using CDC Epi Info 7TM. The estimated new cancer cases of each one of the countries were grouped and considered as an independent population in Globocan 2012. The 10 most common cancer sites from the two populations, study and Globocan 2012, were compared through different non parametric statistical tests, namely the Wilcoxon signed-rank test and the Mann-Whitney U test, using IBM SPSS 15.0 software.

3. Results

During the reporting period, the group of eight comprehensive cancer centres reviewed a total of 17,713 medical records chronologically registered in 2012. Figure 1 shows how eligibility of cancer cases was assessed. Gathered information included 13104 confirmed cancer cases, of which 7106 (54.2%) were eligible and therefore considered as the sample to be analysed.

3.1. Characteristics of the Cancer Centres

In terms of accessibility and availability of services, all centres are integrated in their respective public health care systems and had the main modalities of treatment available in 2012. These services included surgical oncology department with specialized surgeons treating the main solid tumours, adequate number of operating theatres and intensive care unit; operational and well-staffed medical oncology and radiotherapy departments.

All centres had clinical guidelines and/or protocols implemented and tumour boards established for the most common cancer sites. The mean and median estimated waiting time to commence radiotherapy treatment in the group of cancer centres in 2012 was 35 and 33 (range: 7 - 84 days) respectively.

The only private centre participating in the study was a not-for-profit cancer centre where cancer treatment is fully subsidized by the government and that currently treats about 60% of the cancer patients in the country. In all the selected cancer centres, cancer diagnosis and treatment was subsidized by the governments and out-of-pocket expenditure was considered minimal or non-existent.

3.2. Characteristics of the Study Population

From the 7106 eligible cases, 4337 were female (61.0%) and 2769 were male (39.0%). The mean age of the population analysed was 57 years of age (range: 18 - 99 years of age).

The five commonest cancers sites were breast, cervical, oral cavity, colorectal, and lung, which all combined accounted for more than half of the cases. Among women, breast and gynaecological cancers accounted for over 60% of the cancers, whereas among men the top cancer sites were head and neck, prostate, lung, and colorectal. Table 1 shows the most common cancer sites found in the study in both sexes and their respective frequency and distribution in the countries where the cancer centres are located based on Globocan 2012 estimates. The comparison of the distribution of cancer sites between these two populations showed no significant differences. Histopathology was the most valid method of diagnosis in 91.0% of the cases.

At the time of diagnosis over 54.3% of the cancer cases had disease that had spread beyond the primary site, 41.2% were considered as having local disease and in 4.5% of the cases the information on disease extension was unknown. The proportion of females diagnosed with local disease was about 10% higher than in males.

3.3. Treatment Modalities Prescribed

Figure 2 shows the distribution of modalities that were included in the treatment, where each bar corresponds to the combination of single and/or multi-therapy schemes where that particular treatment modality was indicated. Prescription of main cancer treatment modalities were distributed as follows: 57.6% for chemotherapy (n = 4093), 56.8% for surgery (n = 4038), and 46.8% for radiotherapy (n = 3327). Other therapies were prescribed in a small proportion of patients and in the majority of these cases in combination with main modalities; hormonal therapy (12.0%), radio-iodine therapy (2.0%) and immunotherapy (0.9%).
There was a predominance of treatment plans consisting of combination of treatment modalities over mono-
therapy (55.2% versus 44.8%). Overall, the most common combination of treatment modalities involved che-
motherapy and radiotherapy (16.6%) followed by surgery, chemotherapy and radiotherapy (10.8%), surgery and
chemotherapy (9.2%), and surgery and radiotherapy (4.6%). Among treatment modalities prescribed alone, sur-
gery, chemotherapy and radiotherapy accounted for 23.0%, 13.0% and 6.8% of all prescriptions, respectively.
For those patients that had a prescription of radiotherapy, the large majority were planned to receive telethe-
rapy only (74.0%) whilst 8.4% were prescribed to undergo both teletherapy and brachytherapy. Brachytherapy
alone was prescribed in 9.3% of the radiotherapy patients. Information on the type of radiation therapy prescribed was not available in 8.2% of the cases, since in some cases the initial treatment plan did not specify type of radiation therapy. There was no mention of treatment with any other radio-isotope than iodine (I¹³¹).

When grouping patients into sub-populations according to extension of the disease, the findings show variations in prescription among different treatment modalities. As illustrated in Figure 3, the proportion of patients with indications for surgery decreased gradually as disease advances from local to metastatic disease (from 72.8% to 25.7%), in contrast with the prescription of chemotherapy that increased (from 37.2% to 76.1%). The inclusion of radiotherapy in the first treatment plan varied from 41.1%, 61.9% and 31.5% in local, regional and distant tumours, respectively. No major differences were noted in hormonal therapy, radio-iodine therapy and immunotherapy.

4. Discussion

The sample in this study consisted of 7106 new adult untreated cancer patients, excluding non-melanoma skin cancer, consecutively registered in 2012. The results suggest a demand of surgery, chemotherapy and radiotherapy services of 57.6%, 56.8%, and 46.8%, respectively. In addition, hormonal therapy, radio-iodine therapy and immunotherapy were prescribed to 12.0%, 2.0% and 0.9% of the total cancer patients, respectively (Figure 2).

In planning oncology services, the impact on initial investment is more pronounced in radiotherapy than in the other cancer treatment modalities such as medical oncology and surgery, where infrastructure demand is generally determined at the hospital level. In these modalities, costs related to oncology medicines, surgical procedures, hospitalizations and workforce account for a much larger fraction than setting up treatment services. For these reasons, studies aiming at planning oncology services at a national level tend to focus on radiotherapy due to the expected higher capital costs of establishing a new radiotherapy facility. This initial investment could reach 5 - 6 million US$ in developing countries [26]. Studies in developed countries show that equipment and building costs for radiotherapy represent about 30% of the total costs, while wage costs account for about half [15] [27]. In developing countries, however, staffing costs are significantly lower and therefore the proportion of radiotherapy cost related to the establishment of a new facility may be much higher.

The proportion of patients prescribed with radiotherapy in this study is in line with the common benchmark reported in recent years of at least 50% of new cancer patients requiring radiotherapy [20]. Reviewing the available literature, different approaches can be found in Table 2 concerning the estimation of radiotherapy demand in different countries.

In the majority of the studies, the number of patients that received treatment in the radiotherapy departments in a defined period of time was compared to the respective national cancer registry to understand how radiotherapy was being utilized in the care of cancer patients. The results in these assessments varied from 26% in Japan (2007) [19] to 48% in the Netherlands (1997) [14]. The results from the Dutch survey were consistent with the assessment made by the Swedish Council on Technology Assessment in Health Care (SBU) which in 2001 established a radiotherapy utilization rate of 47% in Sweden, 15% higher than in 1992 [11] [15]. Identical approaches with somewhat similar results on radiotherapy utilization rate have been followed in Austria (42%) [16], Italy (41%) [17], and Spain (38%) [13].
Figure 3. Distribution of treatment modalities prescribed according to the extension of the disease (local; regional; distant; unknown).

Table 2. Reported ratios of radiotherapy utilization in different countries/regions.

<table>
<thead>
<tr>
<th>Country or region</th>
<th>Year(s) of assessment</th>
<th>% of cancer patients receiving radiotherapy</th>
<th>Data sources</th>
<th>Cases analysed</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands</td>
<td>1990</td>
<td>47%</td>
<td>α</td>
<td>27,700</td>
<td>Van Daal and Bos, 1997 [10]</td>
</tr>
<tr>
<td>USA</td>
<td>1991</td>
<td>50% - 60%</td>
<td>σ</td>
<td>*</td>
<td>ISCR0, 1991 [9]</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1997</td>
<td>48%</td>
<td>β</td>
<td>31,447†</td>
<td>Slotman and Leer, 2003 [14]</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1997</td>
<td>47%</td>
<td>δ</td>
<td>28,892</td>
<td>Slotman and Leer, 2003 [14]</td>
</tr>
<tr>
<td>Australia</td>
<td>1998</td>
<td>37%</td>
<td>β</td>
<td>9940</td>
<td>Barton, 2000 [12]</td>
</tr>
<tr>
<td>Spain</td>
<td>2000</td>
<td>38%</td>
<td>α</td>
<td>44,505†</td>
<td>Esco et al., 2003 [13]</td>
</tr>
<tr>
<td>Sweden</td>
<td>2001</td>
<td>47%</td>
<td>α</td>
<td>4171</td>
<td>SBU, 2003 [15]</td>
</tr>
<tr>
<td>Austria</td>
<td>2002</td>
<td>42%</td>
<td>α</td>
<td>3783</td>
<td>Ramona et al., 2004 [16]</td>
</tr>
<tr>
<td>Africa</td>
<td>2002</td>
<td>55%</td>
<td>γ</td>
<td>*</td>
<td>Barton et al., 2006 [28]</td>
</tr>
<tr>
<td>Brazil</td>
<td>2002-2004</td>
<td>43%</td>
<td>δ</td>
<td>50,600</td>
<td>Gomes Junior and Almeida, 2009 [29]</td>
</tr>
<tr>
<td>Italy</td>
<td>2003</td>
<td>41%</td>
<td>α</td>
<td>10,560</td>
<td>Pagano et al., 2007 [17]</td>
</tr>
<tr>
<td>Australia</td>
<td>2003</td>
<td>52%</td>
<td>φ</td>
<td>*</td>
<td>Delaney et al., 2005 [20]</td>
</tr>
<tr>
<td>Scotland</td>
<td>2003</td>
<td>46%</td>
<td>β</td>
<td>11,932</td>
<td>Erridge et al., 2007 [18]</td>
</tr>
<tr>
<td>Scotland</td>
<td>2005</td>
<td>44% - 48%</td>
<td>φ</td>
<td>*</td>
<td>Erridge et al., 2007 [18]</td>
</tr>
<tr>
<td>Japan</td>
<td>2007</td>
<td>26%</td>
<td>β</td>
<td>218,000</td>
<td>Teshima et al., 2010 [19]</td>
</tr>
<tr>
<td>England</td>
<td>2007-2009</td>
<td>41%</td>
<td>φ</td>
<td>*</td>
<td>Round et al., 2013 [21]</td>
</tr>
</tbody>
</table>

*: Not applicable; †: External beam radiation sessions; α: Prospective survey in radiotherapy departments; β: Retrospective survey in radiotherapy departments; δ: Governmental report on the use of special medical techniques, including radiotherapy; φ: Decision trees based on evidence-based guidelines and population-based data; γ: Decision trees based on evidence-based guidelines (CCORE model) and estimated population-based data (Globocan 2002); σ: Expert’s opinion.

In the case of the Spanish and Italian surveys, the needs in radiotherapy accessibility were assessed by comparing the findings with an expected radiotherapy utilization rate. In the case of the Spanish survey, Esco et al. proposed a benchmark of 60% of new and prevalent cancer cases needing radiotherapy as part of their treatment plan and calculated the needed resources to fulfill the estimated national demand by comparing with the estimated percentage of cancer cases that received radiotherapy in 1998 (38%). On the other hand, Pagano et al. calculated the gap in radiotherapy in Piedmont region (Italy) by applying the model developed by the Collaboration for Cancer Outcome Research and Evaluation (CCORE), which estimates the optimal radiotherapy utilization rate by combining epidemiological data with decision-trees based on clinical guidelines in Australia [20];
the comparison suggested that the utilization of radiotherapy was about 15% lower than expected if those clinical guidelines would be fully implemented.

The model developed by CCORE and the estimate that 52% of cancer patients in Australia has been used as a gold standard level of radiotherapy utilization in both developed and developing countries. Similar to the Italian survey, this model was applied in the African population and suggested that 55% of the new cancer cases in that continent have an indication of radiotherapy [28]. This utilization rate relied on estimates taken from Globocan 2002, so no information on the staging of the disease was available. The authors further projected that due to the advanced nature of cancer cases at diagnosis, the radiotherapy utilization rate might be even higher in low and middle income countries as advanced tumours are unlikely to be as amenable to surgery and more often treated with palliative radiotherapy.

However, a study conducted in the São Paulo state in Brazil determined that radiation therapy was delivered in just over 40% of new cancer cases and that surgery and chemotherapy were provided to nearly 50% of these cancer patients [29]. In fact, even among high income countries with similar patterns of care and populations, such as Australian and British populations, indications for radiotherapy based on clinical guidelines can vary by about 10% [20] [21]. These disparities suggest that indications for treatment in developing countries derived from guidelines and standards of treatment followed by countries with higher availability of resources should be analysed with caution. In many countries, treatment plans are not supported by evidence although they are considered common clinical practice in some hospitals and the optimal utilization of treatment modalities is often not feasible [30], particularly in resource constrained settings.

Many developing countries are undergoing the process of setting up new radiotherapy services and different approaches have been taken to estimate the needed infrastructure and improve access to treatment. In India, teletherapy needs were calculated based on the benchmark of one cobalt unit per one million population and based on this a shortfall of over 700 teletherapy units was reported in 2006 [31]. In contrast, in Romania a proposal on the expansion of radiotherapy services within the country was planned on the basis that 70% of the new cancer cases require radiation [32]. Although generalizing contexts must be done carefully, in the case of developing countries and having in mind that the IAEA reported that nearly 30 African and Asian countries have no radiotherapy services at all [26], and only 23 African countries are known to have teletherapy [33], it is important to generate information in constrained resources settings to support feasible solutions and to better assist national health planners in the decision making process.

This study which provides estimates of the main cancer treatment modalities prescribed to new cancer cases in developing countries aimed to generate evidence on what is currently realistic and feasible to meet demands on their health systems. More detailed analytical information gathered in constrained resources settings will shed light on the patterns of care and the different elements of access that affect the prescription and utilization of cancer therapies in developing countries.

An important limitation in cancer infrastructure planning in developing countries is the absence or underdevelopment of population-based cancer registries that can provide unbiased estimates of cancer incidence in a well-defined population [34] [35]. As a result, for many of these countries the best and sometimes the only available source of epidemiological information for planning cancer-related services is the Globocan database. This study took this into consideration and the eligibility criteria were therefore established to allow cross-checking with Globocan and therefore provide data that can be useful for health planners in low resource setting. For this reason, the study captured only new cancer cases and excluded non-melanoma skin cancer. In order to overcome a possible treatment modality selection bias effect, only new untreated cancer patients were considered in this study as many cancer patients in developing countries (about 25% of the total cancer cases registered in the study) receive, for example, surgical treatment in a non-comprehensive cancer care centre and are subsequently referred to a specialized hospital to complete the treatment plan with chemotherapy and/or radiotherapy.

Even though there are variations in the GNI per capita (range: 1530 - 11630 USD) [22] and human development index (HDI) (range: 0.554 - 0.786) [36] among the group of countries in this study, the selected centres have similar characteristics in terms of their availability of treatment services including human resources and affordability for patients which are among the main elements of access to cancer treatment. Moreover, the average estimated waiting time to commence treatment in the group of cancer centres is shorter than what has been suggested as the maximum corresponding waiting time tolerated by Australian cancer patients before deciding
to travel to a more distant centre (one week less) or to stay away from home for the duration of treatment (two weeks less) [37].

Considering the similarities among centres, the results obtained should be seen as an approximation of cancer treatment service demand based on what is currently practiced and therefore feasible in developing countries, particularly in middle income countries. Hence, the results are relevant for developing countries that are in the process of creating new or strengthening existent cancer treatment services in the context of a comprehensive national cancer control plan.

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