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CONTENTS

A successful clinical pilot registry of four radiation oncology practices in Africa and Ontario

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Abstract

Objective: Radiation Oncology practices can exhibit heterogeneities between and sometimes within institutions. Clinical registries with scope and detail could quantify consistency and distinctives that justify difference. Retrospective, isolated clinical audits are problematic, typically because not all data are captured in charts, while useful prospective clinical registries will have to be practical, efficient and accurate. We tested feasibility of a clinical registry at a critical time-point in the patient's clinical trajectory when treating physicians could have requisite data.

Design: This was a prospective and non-randomized observational study. Four centres used a 1-page form to acquire data during a 4-month period. Patients had curative breast, rectum or prostate cancers, or were palliative. Objectives were to demonstrate form completion and to delineate patterns of disease presentation and clinical practice.

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Results: The 107 cases had 99% complete data, internally consistent within cases and centres. Similar practices were seen for 22 cases with curative rectal and prostate cancer, and 34 palliative cases, but of the 51 curative breast cancer cases those in Africa were with greater Stage, underwent more extensive surgery, were less likely to receive shorter radiation schedules, and were less exposed to Taxane-based chemotherapy regimens.

Conclusions: This study demonstrates the feasibility for a simple clinical registry requiring minimal effort by participants. A real-time pan-African registry, operating continually or in regular waves, could provide important knowledge at little cost.

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Introduction

Cancer is a major disease category in higher-income countries (HIC), In HIC, health resources are substantial, with budgets for health care exceeding 10% of Gross Domestic Product of large economies. This resourcing is many times higher[1] than that in low-and-middle-income countries (LMIC) where there are fewer infrastructures[2] and less political and socio-cultural support.[3,4] However, cancer is an increasing concern in LMIC's due to improving longevity and the changing prevalences of etiological agents and broader determinants of disease.[3,5,6,7] Indeed, global mortality from cancer exceeds that from tuberculosis, malaria and HIV-AIDS combined[8], and there are many more cancer cases in LMIC than in HIC.[9]

How best to martial and allocate resources to obtain cancer control in LMIC remains to be determined.[10,11] In developed countries, budget allocations and clinical policies are typically well-established and are based on research done at leading "Western" institutions. In contrast, research in LMIC lags[2] with too few loco-regional data to inform practice and decision-making.[4] Consequently, there is persistent debate about whether "Western" research is directly applicable to LMIC contexts (e.g. ICARO, 2009[12]; AFRA 2006[13] and 2010[14]). For example, LMIC cases may have more advanced Stages, and be less tolerant to some aggressive treatments (due to greater co-morbidities, or genomic and nutritional factors), and there may be different economic, socio-cultural and clinical imperatives.[3,4] Differences between countries should modify strategies for cancer control. But are these differences large enough, or sufficiently categorical, to be distinctives, so that "Western medicine and trials are not applicable to Africa"? Heterogeneity of practice, and the extent to which "Western" research may apply, is not presently a focus of research and a research strategy is needed to address the question.

An expanding suite of IAEA randomized clinical trials does incorporate resource-sparing strategies with increasing attention to clinical heterogeneity and questions of tolerance.[15,16] These trials do not pre-judge whether differences are relative or categorical. They strive for international, multi-centre and high quality evidence that is from, and reflects back to, the LMIC context. Another approach to generating evidence that informs debate is to construct clinical registries to quantify practice homogeneities, heterogeneities, and some determinants of variance. Many countries have pathological registries for cancer incidence. In HIC some registries have mortality data[17,18] but most have few or no clinical data; and where a few Staging and treatment variables are captured[19,20], the completeness and validity of those data in HIC are being challenged.[21] Limited studies with proto-registries in Nigeria[22-4] and Malawi[23] have simulated advocacy for national plans to prevent and manage cancer, but most LMIC have no registries, or just pathology registries.[5,6,24,25] Without current survival data in LMIC, the World Health Organization used modelling to convolute "Western" outcomes data with LMIC incidence data from some countries to estimate survival for LMIC.[26] The accuracy of such high-level projections cannot be checked without clinical registry data arising at points of patient contact, in relevant contexts. Unfortunately, recent international registry-based publications have few African contributions.[27,28] The 2011 IARC Volume II report[27] includes only three African data-sets (for The Gambia, Kenya and Zimbabwe) for mortality in just over 3,000 patients and who were diagnosed back in 1993-1997. Although Stage was an optional data field for extraction, it was not reported for these African countries. To identify today's clinical policies and treatments by centre, country and continent, and to quantify any heterogeneities, we need an efficient, standardized and systematic approach to clinical registries.[29,30]

Any clinical registry must be very practical, efficient and accurate. Current population-based cancer registries typically rely on manual, retrospective abstraction and coding from patient hospital or clinic records. Such databases may not be of sufficient quality to provide accurate data, nor provide adequate radiotherapy details to assess technology.[18] To address limitations of existing data collection programs, we designed a small feasibility project to develop a radiation oncology-specific registry that could capture patient and disease characteristics, and radiation-therapy details, in real-time and from treating physicians. By capturing reliable information on treatment delivery and variables that affect treatment decisions, patterns of practice can be easily surveyed to identify gaps in service or diffusion of technologies (e.g. early uptake of new methods). A real-time clinical registry, particularly if it were extended to capture

outcome data, would be of great interest to physicians, policy makers, payers and vendors, and ultimately to cancer patients.[31]

Materials and Methods

An IAEA research methods and statistics training course (Ethiopia, Nov 2010)[14] was attended by over two dozen trainees and staff in radiation sciences and oncology disciplines. One of us (GJ) was a faculty member. Students raised many beliefs, opinions and issues, including impediments to applying "Western" medicine, difficulties conducting research and practice reviews, and worries about pursuing a research career in Africa. Independent of the course and the IAEA, eight RO trainees were contacted to help create the AFrican RES-earch (AFRES) network. We agreed to jointly pilot a small, real-time clinical registry. For this prospective observational study, with no randomization, and no funding, a short protocol was written with a 1-page data collection form. This was not a formal project of the IAEA or part of any IAEA training course.

Main hypotheses were that practices would differ and that cases in Africa would, to be consistent with what are apparently consensus beliefs[12,13,14] (1) have higher clinical Stages; (2) receive more fractions of radiation per course of treatment; and (3) follow reasonable treatment strategies, but that some women with breast cancer in Africa might receive more extensive surgeries (mastectomy and axillary node dissection) and not receive Taxane-based chemotherapies.

Each trainee in Radiation Oncology (three in Africa) and one staff Radiation Oncologist (in Canada) documented patient, disease and treatment data for their own consecutive curative and palliative cases. The single-use form contained absolutely no patient-identifiers. Check-box lists for the requested items included patient characteristics (age decade e.g. 30-39 years, gender), diagnoses and pathologic features, Stages (for breast, rectum and prostate cancer), surgery and systemic therapies, and radiation details (plan type, dose and fractions). Writing was required for only the three dates (consult, and radiation start and end, else "pending").

The form was designed for single-use at one time-point (near or at completion of all acute treatment, or upon a decision against radiation treatment). We specifically chose this time-point as the patient changes phase from treatment to survivorship as a critical time when front-line staff is making decisions and maximum effort is being made by them to assemble data for decision-making and clinical documentation. This presents an opportune time to acquire data that is more accurate and complete. There were no repeat measures as only one form was completed once per case, so this is a study with cross-sectional design. There was no patient selection; all consecutive cases with the requisite diseases of breast, lung, rectal or prostate cancer were included in the study. Forms were submitted systematically (one per patient when completed at the one important time-point where data were readily available) to the Data and Methods Centre in Ontario. No forms or data were dropped from analysis.

Data were analyzed with STATA version 12 (College Station TX). Cases were grouped according to clinical context (e.g. curative), disease type (e.g. breast cancer), and participating centre (AF1, AF2, AF3, and ON1). We assessed how complete were data submissions to the proto-registry using the single-use, 1-page form. Data range and consistency checks were performed to ensure data integrity. To test the main hypothesis that practices would differ in (1) clinical Stages; (2) number of fractions of radiation per course of treatment; and (3) treatment strategies, e.g. surgeries (mastectomy and axillary node dissection) and Taxane-based chemotherapies, Chi-squared and Fischer's Exact Tests were conducted. Since age-decade was collected, no standard error or standard deviation is reported with mean age. Statistical significance means a two-tailed p-value less than 0.05.

Participants obtained local ethics approval. The forms contained no patient identification; therefore all local ethics committees decided that neither verbal nor written patient consent was required. The study was open from December 24, 2010, to May 1, 2011, but some centres obtained ethics approval part-way through this time window for participation, so accrual was more limited in those centres, as their participation began after their respective ethics approvals were obtained. The simple goal was to acquire data on consecutive patients. Investigator-centered data from single individuals at only four institutions cannot be representative of all practices and case-mixes in those institutions and countries (Sudan, South Africa, Zimbabwe, and Canada), but they can provide a window on activities and fulfill the requirements of a pilot, feasibility study.

Results

Patient and disease-context variables are presented (Table I) for 107 forms submitted (one per patient): 62 from the three African centres (AF1, AF2 and AF3) and 45 from the Ontario centre (ON1). Mean age was 54.1 yr, differing by centre ($p = 0.002$, older in ON1). The most common diagnosis was breast cancer (56%) and so 65% of all 107 cases were female, sex differing by centre ($p < 0.0005$). In ascending order, mean ages were breast 48, rectum 57, lung 61, and prostate 65 yr.

Table I: Presenting characteristics of all 107 cases.

	AF1 (n=20)	AF2 n(=20)	AF3 (n=22)	ON1 (n=45)	Total (n=107)
Mean age (yr)	47.0	45.0	58.6	59.1	54.1
Gender:					
Female	17	16	4	33	70
Male	3	4	18	12	37
Breast:					
Curative	14	10	0	27	51
Palliative	3	5	0	1	9
Rectum:					
Curative	0	0	8	4	12
Palliative	1	2	2	0	5
Prostate:					
Curative	0	0	7	3	10
Palliative	1	2	5	1	9
Lung:					
Curative	0	0	0	0	0
Palliative	1	1	0	5	7
Other:					
Palliative	0	0	0	4	4

There was no statistical difference by centre in the proportion of cases managed with curative intent (p = 0.24). There were 73 curative (51 breast, 12 rectal and 10 prostate) and 34 palliative cases (9 breast, 5 rectal, 9 prostate, 7 lung and 4 other). These 107 cases experienced initial consultations by Radiation Oncology services between May 25, 2010, and Apr 26, 2011 (p = 0.002, differing by centre). However, only 13 cases were seen prior to Dec 20, 2010; all 13 were with curative breast cancer (12 in ON1, and 1 in AF1), indicative of differing patterns of referral for breast cancer, and reflecting more real-time multi-disciplinary decision-making in ON1. Excluding breast cases there was no difference in consultation dates for the remaining cases (p = 0.34). Overall, 4 cases were not offered radiation (1 curative breast in ON1 and 3 palliative cases). The remainder of this Results section provides, in sequence, findings for breast curative, other curative, and palliative cases.

Of 51 curative breast cases, 2 had in-situ disease (both in ON1) and 49 had invasive disease (AF1, AF2 plus ON1). Histology was 90% ductal, 6% lobular and 4% other cancer types. As expected[32,33], mean age was 54.8 yr in ON1 and it was lower at 41.7 yr in AF1 and AF2 combined (p = 0.0017). General disease characteristics and treatments for the 49 invasive breast cases are shown (Table II).

Table II: Disease and treatment characteristics for 49 curative breast breast cancer cases.

	AF1 (n=14)	AF2 (n=10)	ON1 (n=25)	p value
Stage of Breast cancer (AllM0):				
Lower	3	1	16	0.003
Higher: N1-3&T4N0	11	9	9	
Estrogen receptors				
Positive	5	8	18	0.063 (n=48)
Negative	8	2	7	
Missing	1	0	0	
Local excision strategy				
Lumpectomy	5	0	22	<0.0005
Mastectomy	9	10	3	
Axillary dissection strategy				
Sentinel Node	0	0	10	0.009
Axillary Node	14	10	14	
None (elderly)	0	0	1	
Any neo-adjuvant treatment				
Yes	13	0	0	<0.0005
No	1	10	25	
Chemotherapy (neoadjuvant Or adjuvant)				
Yes	12	10	15	0.012
No	2	0	10	
Hormone treatment				
Yes	5	8	15	0.089
No	9	2	10	
Radiation volumes				
Tangents-only	3	0	19	<0.0005
3- or 4- Field	11	10	5	
None	0	0	1	
Fractionation schedules				
<17 fractions	3	0	16	<0.0005(n=48)
17-20 fractions	10	8	0	
>20 fractions	1	2	8	
No radiation	0	0	1	

As compared with ON1, in AF1 and AF2 there were statistically greater proportions of cases with: greater Stage; extensive surgery (mastectomy and axillary dissection); applications of chemotherapy (neoadjuvant and adjuvant); extensive volumes of radiation (i.e. loco-regional 3 and 4-field); and larger numbers of fractions (from 18 to 25) of radiation. Trends were also evident for lower proportions of cases in Africa with positive Estrogen receptors and using hormones. Restricting the contrast to the 29 of the 49

invasive cases with highest Stages, statistical differences between African and Ontario centres remained (Table III); African women with higher-Stage breast cancer received more mastectomies, fewer Taxane-based chemotherapies, and more loco-regional radiation techniques (i.e. 3 and 4 field), but there were no differences in extent of axillary dissection, use of hormones or hypofractionation.

Table III: Comparison for only higher stage invasive breast cancer cases.

Treatment	On1 (N=9) %	AF1+AF2 (n=20) %	p value
Mastectomy	11	78	0.0005
Axillary dissection	100	100	Not significant
Taxane-chemo	67	15	0.010
Hormones	44	50	Not significant
3-or4- field radiation	55	95	0.009
Hypofractionation (<17 fractions)	33	15	Not significant

There were 12 curative rectal cases (8 in AF3 and 4 in ON1). Cases were similar in these two centres, and received similar treatment regimens; 10 received neo-adjuvant long-course chemo-radiation of 25 fractions with 7 receiving a boost. However, one case (in ON1) received a neo-adjuvant short-course 5-fraction scheme. There were 10 curative prostate cases (7 in AF3 and 3 in ON1). These were similar and received similar treatments of local or loco-regional radiotherapy, and hormone suppression, strategies consistent with low, intermediate and high risk categories.

There were 34 palliative cases (6 in AF1, 10 in AF2, 7 in AF3 and 11 in ON1) and 91% received palliative radiotherapy to one or more sites. Overall, 50% of the radiation targets were bone metastases (with or without spinal cord compression), 9% were brain, and 35% were other sites (soft-tissue including pelvis or chest). In the three African centres bone was the more likely target (15/23 cases vs. 2/11 ON1 cases, p = 0.006) while soft-tissue was the more likely target in Ontario (8/11 cases vs. 4/23 in AF1, AF2 and AF3 combined). For bone, doses were appropriately 6 Gy in one fraction and up to 20 Gy in 5 fractions, regardless of centre. However, "hi-grade palliation" was administered to two cases with soft-tissue disease in ON1 (54 and 60 Gy, over 6 weeks) using complex 3-D radiation planning with beam rotation and dynamic multi-leaf collimation methods.

In total, the 107 forms were 99% complete in data on initial submission (with the required total data fields numbering 1,874). Date of initial consultation was missing in 3 cases and both estrogen receptor status and type of chemotherapy were missing in 1 breast case. With a cut-off date for form submissions, some cases were "pending" a date for commencing radiation or chemo-radiation, and this was not counted as "missing." Data on each form were logically consistent and demonstrated patterns of care within each centre for disease types and treatment intents.

Discussion

The primary purpose of this project was to assess feasibility of a clinically-relevant registry that could document patterns of disease presentation and (radiation) oncology practice. This would allow comparative analyses and quantification of heterogeneities. Data capture near or at the end of a course of radiation meant that participants had requisite case-data on-hand to complete the 1-page form in under one or two minutes. Strengths of this project are simplicity, consecutive cases, cross-sectional design that captured longitudinally emergent data (e.g. treatment completion), immediate relevance (i.e. data from 2011), and testing of hypotheses. Local ethics boards did not require patient consent as this study was of low risk to patients. Our findings support a relative homogeneity in important variables for curative rectal and prostate cancer, and for managing bone and brain metastases. However, one rectal cancer in Ontario was hypo-fractionated and two palliative cases with soft-tissue masses were managed with technically complex high-dose approaches in Ontario. In contrast, there was heterogeneity in disease and treatment characteristics for curative breast cancer cases, even treatment differences within those cases with more advanced Stage. Differences were observed between African and Ontarian centres, but AF1 used neo-adjuvant strategies in contrast to AF2 which did not.

Given a small sample size, it was a surprise to discover statistically significant differences. If these were confirmed in a larger, wider project, they would need appropriate explanation.[34] Some differences may reflect a slow diffusion of "Western" technologies. With breast cancer there are several recent changes in North America, to: sentinel node dissection; third-generation Taxane-based chemotherapies for some cases; more extreme hypo-fractionated radiation schedules, that spare radiation resources; and multi-disciplinary discussions early on in a patient's clinical course.[35,36] Conversely, treatment differences can be intentional and entirely appropriate to context. Influencing variables may include patient preference, socio-cultural and economic aspects, travelling distances or costs, Stage-prognostic-factor combinations, radiation machine types and planning systems, and physician training and familiarity with a

few techniques that may give equivalent clinical outcomes as other techniques, methods that are less familiar to the local physician. Investigation of heterogeneity can lead to three outcomes: it should affirm current practice differences; it should result in changes that increase uniformity to best practice[34], or it should prompt research, especially randomized clinical trials that are timely and relevant to those participating in a registry.

Important limitations of this pilot project are the small number of participants (four) and cases (one hundred and seven). Findings can in no way be representative of general practices within the four institutions and countries. Participants had no assistance from program managers or site-coordinators. This project did not set out to gain longer-term data and we did not document on-treatment or subsequent adverse events (AE), disease control or survival. For the acute phase of management, a single process to capture data assembled when there is high-attention by front-line staff, i.e. at a critical time-point, should minimize missing data and maximize efficiency and accuracy. Critical time-points are when there are irreversible decisions being made (e.g. for treatment, or when approving complex radiation plans) or when patients are making key transitions (e.g. entering survivorship, or when experiencing an adverse outcome). Extending to capturing outcome data, linking to pathology and death registries, and merging in some health record and treatment planning details from respective soft-ware sources, could be considered. Electronic form(s) with internal validation and direct e-mail submissions with automated aggregation at a data centre would improve on our pilot study.

A robust, real-time clinical registry (i.e) a true technology, a product and process, to assist font-line practitioners[37]--could have many benefits that align with the goals of the IAEA, including building a broad infrastructure for loco-regional studies, training in loco-regional contexts, evolving evidence-based practices in Radiation Oncology, and in-country advocacy. Most important, Radiation Oncologists with little academic and research infrastructure could easily participate for just a few minutes a day. A clinical registry can document practice consistency, treatment methods, effectiveness, applications of guidelines, and research-relevant skills (e.g. form completion, follow-up, recording AE). These would fulfill probationary requirements to participate in multi-centre, international trials. Data aggregation and analysis can be centralized, using software to automate analyses and reporting, and to assure reproducibility. Regular reports to participants can provide materials and visuals for local presentations, training of staff, discussions on policies, and advocacy. Some participants could proceed to publications. Training in research methods and statistics "in context" (i.e. in daily practice) is known to be more efficient and complete, with a greater level of transfer into local practice, reflection and research.[38] A registry could also provide supplementary documentation for external auditing (e.g. Quality Assurance Team for Radiation Oncology[39]), or hospital accreditation, and international organizations could avoid relying on modelling,[26] historical data,[27] or "pulse-taking" surveys to obtain a sense of current patterns of practice. Regarding surveys, practice within North America and Europe is reverting to using hypo-fractioned, shorter courses of radiotherapy, based on results from "Western" randomized trials: 16 instead of 25 fractions for breast cancer[40] and 5 instead of 25 fractions for some rectal cancers.[41] To justify two on-going randomized trials in LMIC[15,16] of the agency staff had to conduct surveys of potential investigators to assess uptake or interest in hypo-fractionation--for breast in 2005 and for rectum in 2008, because there were no summarizing data from international clinical registries. Our pilot registry, in 2011, confirms that these two studies remain relevant for the context of at least a few countries in Africa.

Future steps are to scale-up this pilot clinical registry. Secondary research questions include how the process of participation and practice-feedback improves clinical care and research infrastructure. Can clinical registries with current data accelerate local and international research relevant to LMIC? Ultimately, a good balance must be struck between adopting HIC or "Western" evidence and generating LMIC evidence and this requires correcting the present asymmetry of data collection (in 2011: more in HIC; less in LMIC). A relatively inexpensive continuous clinical registry, or one conducted in periodic waves, is a good start.

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