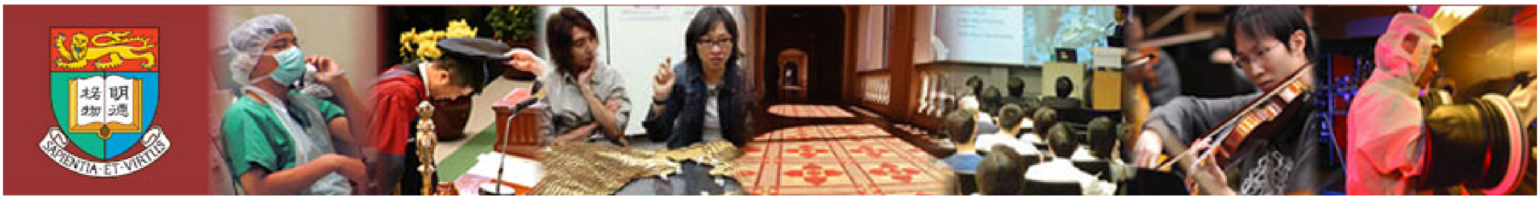

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Clinical Investigation

Global Pattern of Nasopharyngeal Cancer: Correlation of Outcome With Access to Radiation Therapy

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Summary

Nasopharyngeal cancer is highly treatable with radiation therapy, but the treatment outcome varies widely across the world. Eighty percent of new cases occurred in countries with poor outcome. This study showed a significant correlation between outcome and access to radiation therapy. The global inequity of access and the need for optimal service planning are highlighted. It is hoped that this work will help stimulate an international effort toward improving the outcome for nasopharyngeal cancer worldwide.

Objective: This study aimed to estimate the treatment outcome of nasopharyngeal cancer (NPC) across the world and its correlation with access to radiation therapy (RT).

Methods and Materials: The age-standardized mortality (ASM) and age-standardized incidence (ASI) rates of NPC from GLOBOCAN (2012) were summarized, and [1 −(ASM/ASI)] was computed to give the proxy relative survival (RS). Data from the International Atomic Energy Agency (IAEA) and the World Bank were used to assess the availability of RT in surrogate terms: the number of RT equipment units and radiation oncologists per million population.

Results: A total of 112 countries with complete valid data were analyzed, and the proxy RS varied widely from 0% to 83% (median, 50%). Countries were categorized into Good, Median, and Poor outcome groups on the basis of on their proxy RS (<45%, 45%-55%, and >55%). Eighty percent of new cases occurred in the Poor outcome group. Univariable linear regression showed a significant correlation between outcome and the availability of RT: proxy RS increased at 3.4% ($P<.001$) and 1.5% ($P=.001$) per unit increase in RT equipment and oncologist per million population, respectively. The median number of RT equipment units per million population increased significantly from 0.5 in the Poor, 1.5 in the Median, to 4.6 in the Good outcome groups, and the corresponding number of oncologists increased from 1.1, 3.3 to 7.1 ($P<.001$).

Conclusions: Nasopharyngeal cancer is a highly treatable disease, but the outcome varies widely across the world. The current study shows a significant correlation

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between survival and access to RT based on available surrogate indicators. However, the possible reasons for poor outcome are likely to be multifactorial and complex. Concerted international efforts are needed not only to address the fundamental requirement for adequate RT access but also to obtain more comprehensive and accurate data for researches to improve cancer outcome.

Introduction

Epidemiologic data from GLOBOCAN by the International Agency for Research on Cancer (IARC) showed that the total number of new cases of nasopharyngeal cancer (NPC) in the world was 86,691 and the total number of deaths was 50,831 in the year 2012 (1). This cancer has a skewed geographic distribution: 81% of new cases occurred in Asia and 9% in Africa. In terms of the actual number of new patients, the top 5 countries were China, Indonesia, Vietnam, India, and Malaysia, which together accounted for 67% of the global burden (Fig. 1).

This cancer was invariably lethal in the past before the advent of megavoltage radiation therapy (RT). Access to good-quality RT is a fundamental need for treating NPC; with accumulation of knowledge, advancing technology for accurate delineation of disease extent and irradiation techniques, and the addition of potent chemotherapy, 5-year survival rates >80% can now be achieved for patients treated in major centers (2).

There is marked variation in the availability of RT facilities and the quality of service among different countries. The capital and expertise required for providing a proper RT infrastructure represent a major health challenge in low-income and middle- income countries (LMICs). A study by Datta et al (3) showed that only one third of the global teletherapy units exist in LMICs to treat nearly 60% of the world's cancer patients. Published articles analyzing access to RT in different regions mostly estimate the needs based on the number of cancer cases and RT utilization rates, or comparison of available RT resources against benchmarks (4, 5). The current study is the first attempt to link RT access with survival outcome, using NPC as an example. Q1

Methods and Materials

Estimation of survival outcome

Most of the cancer registries in countries where NPC is prevalent do not have detailed individual patient records with prospective follow-up data. The best available indicators of the disease burden in each country are the age-standardized mortality (ASM) and age-standardized incidence (ASI) rates from GLOBOCAN 2012 (1). Inasmuch as a previous study has shown that [1−(ASM/ASI)] is a good approximation of the 5-year relative survival (RS) for most tumor sites (6), this was used to compute a proxy RS for comparison of treatment outcomes among different countries.

Information on access to radiation therapy

Information on the availability of RT facilities and personnel in different countries was retrieved from the Directory of Radiotherapy Centers of the International

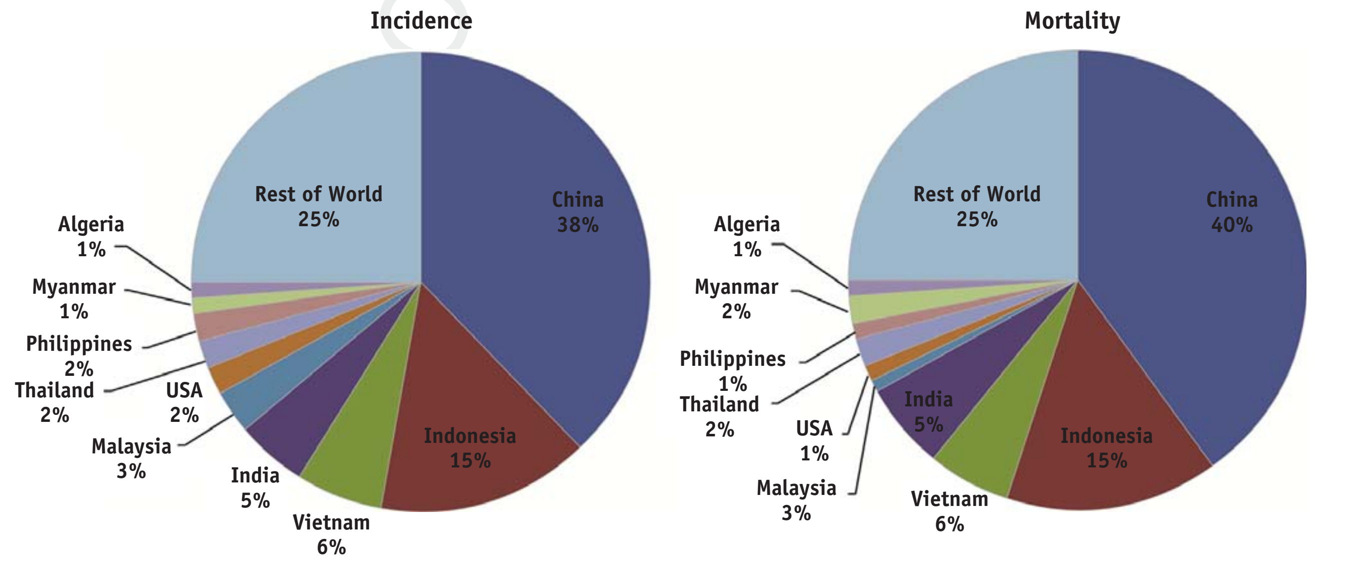

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Fig. 1. Epidemiologic pattern of nasopharyngeal cancer: total number of new patients and deaths by countries. (Data from GLOBOCAN 2012).

Atomic Energy Agency (IAEA-DIRAC) (7). The total populations of different countries in 2012 were retrieved from The World Bank database (8). Two surrogate indicators were calculated to reflect the access to RT: the number of RT equipment units (linear accelerators, cobalt units, or both) and the number of radiation oncologists per million population.

Inclusion and exclusion criteria

Countries in each continent (Asia, Africa, America, Europe, and Oceania) were identified; all those with complete ASM, ASI, equipment, oncologist, and population data were reviewed. Countries without RT facilities and gross outliers with concern about the quality of epidemiologic data (ASM/ASI ratio equal to zero or exceed 1) were excluded from the analysis.

Statistical analysis

To evaluate the correlation of survival outcome with RT facilities and personnel, univariable linear regression was performed with proxy RS as the dependent variable, and RT equipment and oncologists as independent variables separately. The coefficients of determination (R^2) and the regression coefficients (β) were measured. In addition, countries were divided into 3 outcome groups (Poor, Median, and Good) based on the proxy RS, and the medians of the RT indicators between the groups were compared by Mood's median test. All statistical analysis was performed with IBM SPSS Statistics 20.0.

Results

Of the 128 countries with complete data on RT indicators, 16 outliers were excluded because of concern about the quality of epidemiologic data (proxy RS less than 0% or equal to 100%). A total of 112 countries with complete valid data (33 from Asia, 21 from Africa, 22 from America, 34 from Europe, and 2 from Oceania) were included in the current analyses. The total number of new patients in these countries was 82,127 (95% of the global burden).

The outcomes varied widely among countries: the proxy RS ranged from 0% to 83% (median, 50%). When a proxy RS of 45% to 55% was taken as an average achievement, countries could be categorized into Poor, Median, and Good outcome groups based on proxy RS <45%, 45% to 55%, and >55%, respectively (Table 1). Different continents showed different proportions of countries categorized into the 3 groups: only 18% (6/33) of countries in Asia and 5% (1/21) in Africa had Good outcome compared with 53% (18/34) in Europe.

Inasmuch as most of the countries with Poor outcome had a high incidence of NPC, the total number of new patients in the Poor outcome group was 69,012 (80% of the global burden). Among the 48 countries with Poor outcome, the 14 countries with incidence >500 new patients in the year 2012 already accounted for 75% of the global burden (Table 2).

The availability of RT varied widely across the world: the number of RT equipment units ranged from 0.02 to 12.6 (mean, 2.6; median, 1.6) per million population; 63 countries (56%) had <2 RT equipment units per million population. The number of radiation oncologists ranged from

Table 1 Summary of different outcome groups

	Outcome groups			
	Poor	Median	Good	*P*
Total no. of new cases	69,012	4599	8516	
Proxy relative survival				
Range	0-43.8%	5.5-52.6%	55.6-83.3%	
Mean ± SD	20.5 ± 15.6%	49.6 ± 1.4%	66.3 ± 8.0%	
Median	25%	50%	66.7%	
Continent, countries				<.001
Asia	14	13	6	
Africa	16	4	1	
America	8	9	5	
Europe	10	6	18	
Oceania	0	1	1	
All	48	33	31	
Equipment/million				<.001
Mean ± SD	1.12 ± 1.66	2.45 ± 2.23	4.93 ± 2.81	
Median	0.50	1.49	4.56	
Oncologists/million				<.001
Mean ± SD	2.77 ± 3.86	4.68 ± 4.40	7.84 ± 4.47	
Median	1.05	3.32	7.14	

Abbreviation: SD = standard deviation.

Table 2 Summary of countries with poor outcome and moderate to high incidence

Country	No. of patients		Age-standardized rate		Proxy RS (%)	Access to radiation therapy per million population	
	New cases	Deaths	ASI	ASM		Equipment	Oncologists
China	33,198	20,404	1.9	1.2	36.8	1.13	5.27
Indonesia	13,084	7391	5.6	3.3	41.1	0.16	0.17
Vietnam	4931	2885	5.4	3.3	38.9	0.42	1.26
India	3947	2836	0.4	0.3	25.0	0.42	0.29
Thailand	1864	1114	2.1	1.3	38.1	1.24	1.08
Philippines	1738	873	2.2	1.3	40.9	0.40	1.89
Myanmar	1148	785	2.4	1.8	25.0	0.13	0.44
Algeria	1083	548	3.2	1.8	43.8	0.49	0.88
Nigeria	1062	744	0.8	0.6	25.0	0.08	0.18
Pakistan	795	532	0.6	0.4	33.3	0.31	0.17
Kenya	784	500	3	2.1	30.0	0.14	0.25
Morocco	726	428	2.3	1.4	39.1	0.95	3.26
Tanzania	531	371	1.8	1.4	22.2	0.04	0.13
Sudan	531	400	2.3	1.8	21.7	0.27	0.51

Abbreviations: ASI = Age-standardized incidence rate; ASM = Age-standardized mortality rate; Proxy RS = Proxy relative survival.

0.03 to 20.5 (mean, 4.7 median, 3.2) per million population. There were 55 countries (49%) with <3 radiation oncologists per million population.

Univariable linear regression showed a statistically significant correlation between proxy RS and both RT access indicators (Fig. 2): a unit increase in RT equipment per million population was associated with an absolute increase of 3.4% (95% confidence interval [CI], 1.97-4.88) in proxy RS ($P<.001$, $R^2 = .166$), whereas a unit increase in oncologists per million population was associated with an absolute increase of 1.5% (95% CI, 0.60-2.33) in proxy RS ($P=.001$, $R^2 = .093$).

There were significant differences in RT facilities and personnel among the 3 outcome groups ($P<.001$) (Fig. 3). The median number of RT equipment units per million population increased from 0.5 in the Poor, 1.5 in the Median, to 4.6 in the Good outcome groups; the corresponding number of oncologists increased from 1.1, 3.3 to 7.1 (Table 1).

Discussion

Global surveillance of cancer survival is increasingly advocated to stimulate health policy and reduce inequity (9, 10). GLOBOCAN 2012 by IARC of the World Health Organization provides the best updated estimates of the incidence, mortality, and prevalence of major cancer at a national level (1). These data are useful for comparison of cancer burden in different countries. However, it should be noted that the quality of the estimation varies depending on the availability of incidence and mortality data and the methods of estimation used for each country.

Accurate calculation of cancer survival requires detailed individual patient records with prospective follow-up data. Unfortunately, most cancer registries (particularly those in LMIC) cannot provide such data. The best possible surrogate currently available for outcome estimation is [1−(ASM/ASI)]; as shown in the study by Vostakolaei et al (6) on 32 cancer sites in 7 different countries, this indicator is a good approximation of 5-year relative survival for most sites.

It is well known that the overall outcome for cancer patients in LMIC is substantially poorer than that achievable in developed countries. The possible reasons for poor outcome in any individual country are likely to be multifactorial and complex. However, the data for supporting a more exact analysis of the effect of all possible factors from cultural, geographic, and socioeconomic issues to all aspects of health care provision from diagnoses, staging, and cancer treatment modalities to supportive care are lacking and are unlikely to become available in the near future.

Of all these factors, inadequate access to RT facilities is one of the key problems. It is worthwhile to start studying this serious problem because RT is increasingly used as a definitive treatment modality for many cancers, and the setup of RT services involves comprehensive planning and high capital cost. Currently, the only source of information about RT access is the DIRAC-IAEA (7), which is a registry of the number of RT equipment and staff members in different countries based on continuous update by member states. However, it should be cautioned that the data are based on voluntary reporting, and there is no information on quality of RT (for example, the machine capability for conformal/intensity-modulated techniques and quality assurance). Furthermore, accurate comparison of staffing across countries is especially difficult because of variations in the scope of services by oncologists (confined to radiation oncology alone in some countries, but covering both radiation and medical oncology in others). Concerned with this pitfall, IAEA has suspended the release of staffing information to the public, and efforts are now being taken to address this issue.

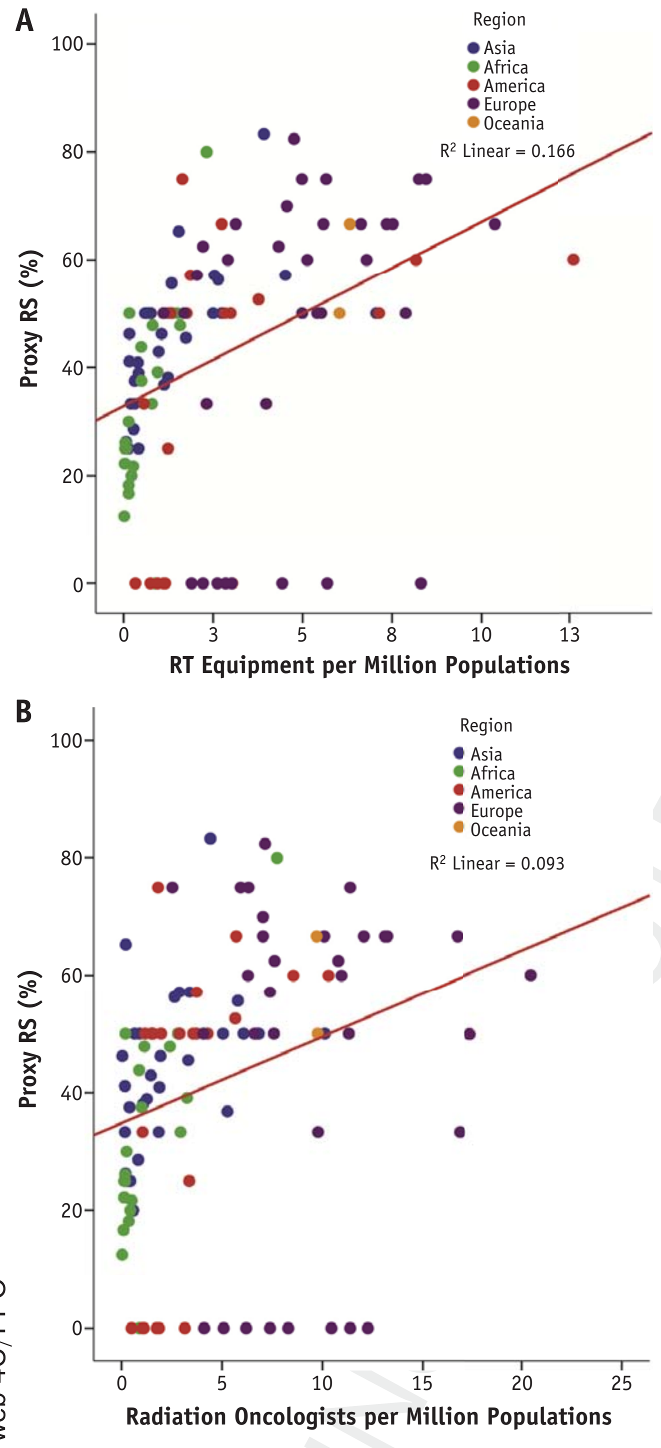

Fig. 2. Correlation of proxy relative survival with (A) radiation therapy (RT) equipment and (B) radiation oncologists per million populations by univariable linear regression.

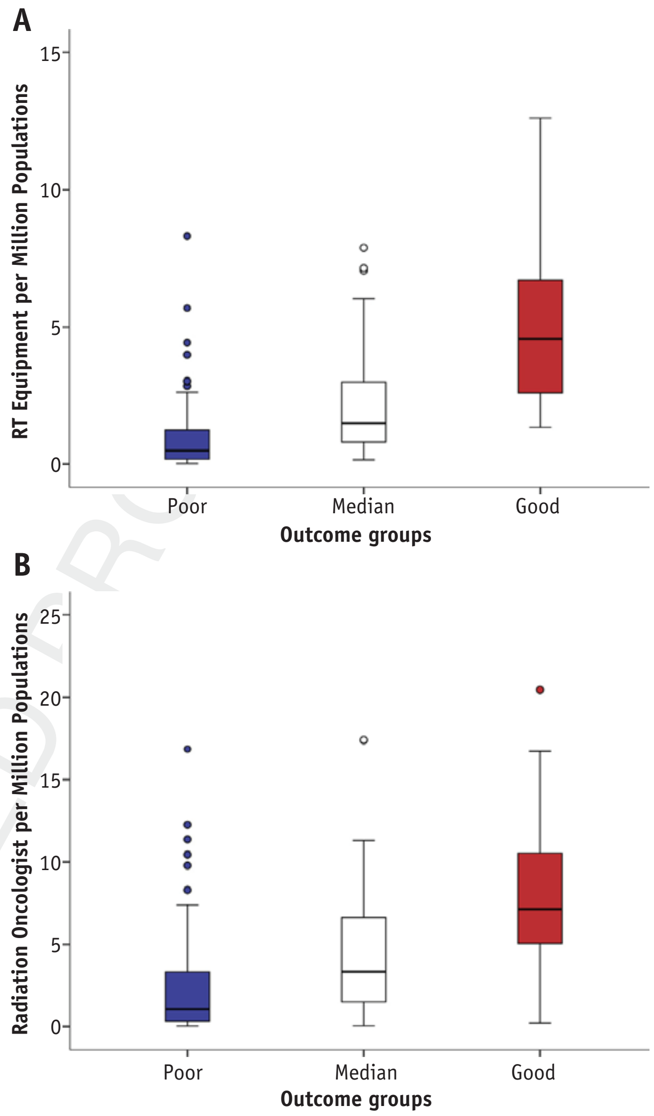

Fig. 3. Comparison of radiation therapy (RT) access indicators in different outcome groups. (A) RT equipment and (B) radiation oncologists per million population.

Naturally, the RT facilities in a country are used for all indicated cancers rather than a specific cancer, but for analysis of the correlation between RT access and cancer outcome, inclusion of all cancers is not adopted because heterogeneity in the RT utilization rates. NPC is one of the best cancers for analyzing the link because this is a highly curable cancer and RT is the fundamental treatment modality; the RT utilization rate is 100%, surgery is used only for salvaging persistence/recurrence, and the absolute magnitude of increase in 5-year overall survival by adding chemotherapy is only 6% according to the latest meta-analysis (11).

The current study showed a marked variation in outcome of NPC among different countries: the proxy RS ranged from 0% to 83%. Countries can be divided into Poor, Median, and Good outcome groups on the basis of proxy RS (Table 1); only 18% of countries in Asia and 5% in Africa had proxy RS >55%. For the 48 countries in the Poor outcome group, the median proxy RS was only 25%. Most unfortunately, these countries are those with the highest incidence of NPC; 69,012 new patients were registered in these countries in the year 2012, accounting for 80% of the global burden. The social consequences are clearly enormous because the peak incidence occurs at 40 to 50 years of age in endemic countries.

Table 3 Summary of results from 3 representative studies in Hong Kong

		Staging investigation				Stage*	RT technique				Chemotherapy		5-year
Study	Year	X-ray	CT	MRI	PET	III-IVB	2D	3D	IMRT	Total dose	Concurrent	Not concurrent	DSS
Lee et al, 1992 (16)	1976-1980	100%	0.1%	0	0	72%	100%	0	0	81% > 60 Gy	0	7%	47%
	1981-1985	72%	28%	0	0	73%	100%	0	0	91% > 60 Gy	0	11%	57%
Lee et al, 2005 (17)	1996-2000	0	100%	0	0	47%	96%	4%	0	4% > 66 Gy	9%	10%	79%
		0	0	100%	0	65%	78%	22%	0	49% > 66 Gy	23%	9%	83%
Lee, 2014 (8)	1994-1998	0	84%	16%	0	59%	100%	0	0	All 66 Gy	20%	16%	78%
	1998-2005	0	2%	98%	0.3%	85%	0	100%	0	All 70 Gy	55%	3%	81%
	2005-2010	0	0	100%	25%	92%	0	0	100%	All 70 Gy	87%	2%	85%

Abbreviations: CT = computed tomography; DSS = disease-specific survival; IMRT = intensity-modulated radiotherapy; MRI = magnetic resonance imaging; PET = positron emission tomography; RT = radiation therapy.
* Stage by AJCC/UICC, 5th edition.

There is marked inequity of access to RT across the world: the number of RT equipment ranged widely from 0.02 to 12.6 per million population. The current study demonstrated a strongly significant correlation between access and outcome (Table 1, Figs. 2 and 3). The median number of equipment units was 0.5 in the Poor outcome group compared with 4.6 in the Good outcome group. Similarly, the number of radiation oncologists ranged widely from 0.03 to 20.5 per million population: the corresponding median number of oncologists was 1.1 in the Poor outcome group compared with 7.1 in the Good outcome group. Improvement of access to RT is a fundamental issue to be addressed for helping the Poor outcome countries.

This study is the first attempt to link RT access with survival outcome. Although there are limitations because the current findings are based on surrogate indicators and other confounding factors affect outcome, nevertheless, this attempt provides a vivid example to reflect the current unfortunate situation in LMIC. Furthermore, this could contribute to a call for more comprehensive international data and stimulate global health research to develop sustainable health policy for improving cancer care.

Besides the problem of access, the quality of RT and the overall pattern of care are also important. There are wide variations in treatment results achieved by different centers. This is highlighted by a prospective randomized trial conducted by IAEA, which aimed to evaluate the addition of a brachytherapy boost in patients with advanced NPC treated by standard chemoradiation therapy (12). A total of 274 patients from participating centers in Egypt, Algeria, Morocco, Pakistan, and Thailand during the period 2004 to 2008 were studied. The 3-year results showed no significant improvement in local failure-free survival by adding brachytherapy. The key concern was that local control was poor even in patients with T1-2N+ disease (58% with brachytherapy vs 52% without brachytherapy, $P=.34$).

Reports from a center at Yogyakarta in Indonesia, the country with the second largest number of new NPC patients, revealed even more disturbing findings: the complete response achieved for NPC patients was only 29%, and the median overall survival was less than 2 years (13). A detailed analysis of patients treated with curative RT from 2011 to 2012 showed that long diagnosis-to-treatment intervals and prolongation of overall treatment time were the major contributory factors to the poor treatment outcomes (14). The main causes of the prolongation included malfunctioning equipment, modification of radiation fields, public holidays, power blackout, and patients' poor condition or preference. These illustrate the multifactorial nature of difficulties leading to poor outcomes at centers in LMIC.

Even in centers from developed countries, the importance of the quality of RT cannot be overemphasized. A corollary finding in the TROG 02.02 (HeadSTART) Trial, which aimed to evaluate the therapeutic benefit of tirapazamine for advanced head and neck carcinoma, showed that patients with major deficiencies in their treatment plans had a markedly inferior outcome than did patients whose treatment was protocol compliant: the 2 years overall survival was 50% versus 70%, and the locoregional failure-free rate was 54% versus 78% ($P=.001$) (15).

Another important factor is the overall pattern of care from diagnosis to completion of therapy. Experience from Hong Kong demonstrates a steady improvement in outcome with evolving advances (Table 3), as shown by 3 representative studies during different periods (2, 16, 17). The increasing use of more accurate staging investigation by magnetic resonance imaging and positron emission tomography, more conformal RT using the intensity-modulated technique, optimal dose fractionation, and the addition of concurrent ± sequential chemotherapy for patients with locoregionally advanced disease all contributed to achieving the contemporary best results. The most encouraging message is that a 5-year survival of 50% is achievable even with staging by x-ray and treatment by 2-dimensional RT alone. This highlights the importance of other contributory improvements and the results achievable within the limitation of resources as our services evolve.

The current analysis has started to attract international interest. The IAEA is now launching a coordinated research project to improve the outcomes of NPC in LMIC. The 14 countries with Poor outcome and moderate to high incidence (Table 2) will be the key targets for improvement because 75% of global new patients occur in these countries. The project will include a national survey for more comprehensive data of RT facilities, a cross-sectional study on patient characteristics, the pattern of care, the quality of RT planning and clinical outcome in representative centers, and a comparative study to explore for outcome improvement by educational intervention and the establishment of quality review processes. It is hoped these international efforts can help to stimulate government in Poor outcome countries to improve service provisions and less experienced centers to improve their quality of RT so that the maximum number of patients can be cured.

It is concluded that NPC is highly curable, but the outcomes varied widely; unfortunately, 80% of patients with new diagnoses were in LMIC with poor outcome (proxy RS <45%), The current study is the first attempt to correlate the outcome with RT resources based on available surrogate indicators (proxy survival from data by GLOBOCAN 2012, number of external RT equipment and radiation oncologists from IAEA-DIRAC). It is important to start studying the serious problem of RT access because this is a fundamental requirement; the setup of RT services involves comprehensive planning and high capital cost. There is little doubt that outcome could also be affected by other confounding factors, but the data necessary for supporting a more exact analysis of the effect of all possible factors are currently unavailable. This report is a starting step to call for concerted international efforts to address not only the inequity of RT access in LMIC but also the need for more comprehensive and more accurate data for health care research, to draw the attention of policy makers to develop sustainable health policy for improving cancer care.

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