ORIGINAL RESEARCH

Cost-utility and cost-consequence analysis of different cervical cancer therapies received by patients in two Nigerian tertiary hospitals

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ABSTRACT

Background: High treatment costs pose a lot of economic burden on cervical cancer (CC) patients and their family members. Studies on cost-utility and cost-consequences analysis of CC therapies are lacking in Nigeria.
Objective: To evaluate the cost-utility and cost-consequence of different CC therapies received by patients in two Nigerian tertiary hospitals.
Method: This study employed a prospective longitudinal design with a 12-month patient follow-up. It was conducted at Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto and Ahmadu Bello University Teaching Hospital (ABUTH), Zaria, North-Western Nigeria. Data of all the 157 eligible CC patients were collected at baseline, after therapy and at 12 months follow up. Data analysis was done with appropriate descriptive and inferential statistics using SPSS V. 20 for windows. $P<0.05$ was considered statistically significant.
Results: The mean total cost of therapy per patient for adjuvant chemoradiation therapy (CRTS) was the highest (₦663,497±164,690). The incremental cost-utility ratio (ICUR) for adjuvant chemotherapy (CTS) was the lowest (₦529,042 per QALY), while CRT had the highest ICUR, ₦9,511,087 per QALY. Adjuvant radiotherapy (RTS) had ₦452,009±10,619 mean total cost per patient against best symptoms' resolution and survival; unfortunately, fertility not preserved.
Conclusion: Adjuvant chemotherapy (CTS) was found to be the most cost-effective therapy option, while CRT was found to be least cost-effective therapy option received by the patients. Adjuvant radiotherapy (RTS) had a moderate mean total cost per patient with the best symptoms' resolution and survival; unfortunately, fertility not preserved.

Keywords: Cervical Cancer; Therapies; Cost-Utility; Cost-Consequences; Cost effectiveness

INTRODUCTION

High treatment costs pose a lot of economic burden on CC patients and their family members[1]. According to the Intercontinental Medical Statistics (IMS) report, the global spending on oncology medicines broke the $100 billion threshold in 2014[2]. Some cancer registries in Nigeria also reported similar and relative high treatment costs[2,3]. A cost-effectiveness analysis study showed cisplatin + paclitaxel as an acceptable alternative to cisplatin alone for the treatment of advanced or recurrent CC patients with an increase in cost of only $13,654/QALY. The addition of topotecan did not increase survival enough to justify the increased cost[4]. Another similar study showed

that, the combination of 5FU and irinotecan (whether used first or second line) appears to be more cost-effective than the single agent sequential therapies, or 5FU plus oxaliplatin[5]. A study conducted in Thailand showed that, radical hysterectomy with pelvic lymph node dissection (RHPLND) provides better value for money than concurrent chemoradiation therapy (CCRT) and therefore, an efficient treatment for stage IB CC[6]. A study conducted in Ontario showed that, the mean overall medical care cost for CC was $39,187 in the 1st year after diagnosis[7].

Similar economic evaluation studies on CC therapies given based on the availability of our health care resources and patients' economic capacities are needed. This is because, results of studies from other countries may not translate to what is obtainable in Nigeria due to our economic and infrastructural differences. For instance, well organized early detection programs coupled with effective treatment modalities, have shown to reduced deaths from CC by up to 70% in developed countries. However, attainment of similar results in Nigeria and other Sub-Saharan African countries is hampered by insufficient funds often attributed to competing health priorities, weak health systems and limited numbers of trained providers. For the above-mentioned reasons, this study was conducted to evaluate the cost-utility and cost-consequence analysis of different CC therapies received by patients in two Nigerian tertiary hospitals.

METHODS

Study design and settings

This study used a prospective longitudinal design with a 12-month patient follow-up. It was conducted at Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto in Sokoto state and Ahmadu Bello University Teaching Hospital (ABUTH), Zaria in Kaduna state, North-Western Nigeria.

Study participants and eligibility requirements

Patients diagnosed with CC and treated with chemotherapy, radiotherapy or both, with or without surgery were included in the study. Patients who were treated with surgical intervention alone were excluded from the study. Patients with adequate baseline information were included, and those who started treatments and referred from facilities other than ABUTH or UDUTH and whose baseline information could not be obtained were excluded from the study. Patients who could not respond to interviews due to severity of the illness and those who declined consent to participate in the study were also excluded.

Sampling technique

All eligible patients who came to the Radiotherapy and Oncology clinics of the hospitals were recruited during the six months recruitment period (January - June 2019).

Study instruments

Pro Forma: This consisted of four (4) sections (A-D). Section A: consisted of the patient's socio-demographic information, B: base-line clinical profile of the patient, C: treatment(s) received and D: follow-ups.

A Generic 15D© Quality of Life Questionnaire[8]*:* The 15D is a generic, comprehensive, 15-dimensional, standardized, self-administered measure of health-related quality of life (HRQoL) that can be used both as a profile and single index score measure. The instrument was used to collect data of the patients' QoLs before and after therapy. The 15-domains include: Mobility, Vision, Hearing, Breathing, Sleeping, Eating, Speech, Excretion, Usual Activities, Mental Function, Discomfort and Symptoms, Depression, Distress, Vitality and Sexual Activity domain. Each domain has five question items (1 to 5) with the first question item indicating the best, while the last indicating the worst QoL.

The HRQoL provide utility (preference) scores on a generic scale where dead = 0.00

and perfect health = 1.00. One of the most commonly used units of utility is quality-adjusted life years (QALY) which can be computed from the utility scores of overall HRQoL of patients, and then used in cost-utility and cost-effectiveness analyses.

Study procedure

Research assistants were recruited and trained using all relevant materials such as the study instruments, sample patient's folder and the radiation cards, to ensure quality data collection. The economic evaluation perspective was that of the patient, hence, only direct health service costs were included. These included treatment costs (including treatment related adverse events (AEs)), costs of visits to a specialist or nurse based on 'standard practice' assumptions and the costs of hospital bed occupancy. Non-medical costs such as out-of-pocket expenses incurred when visiting clinics, cost of informal care provided by family members and production losses resulting from work absences, long-term disability (including fertility loss) or premature death were not included in the evaluation as information on them were not readily available. The unit costs to resource volumes used (drugs and other consumables, laboratory tests, clinic visits, and specialty care per visit) were derived using NHIS price list, 2nd edition 2013[9]. The costs of all inpatient bed-days were derived from 2005 WHO-CHOICE Estimates of Unit Costs for Patient Services for Nigeria[10]. All costs were adjusted using 2019 consumer price index (CPI). We compared the recommended therapy options by international guidelines to the most available therapy options in the study area as alternatives. QoL data were collected via self-administration of the 15D QoL instrument at baseline and after the patient completed or due to have completed prescribed therapy option.

For the cost-utility analysis (CUA), the incremental net cost and net effectiveness were calculated in relation to the comparator and expressed as incremental cost-utility ratio (ICUR). QALYs was used as a common health outcome measure. The impact of each therapy option on quality of life was estimated using the 15D HUI questionnaire at baseline, and at 12 months follow up. The difference in QALY for the different treatment groups was estimated.

For the cost-consequence analysis (CCA), the mean total costs of each therapy option per patient in Nigerian naira (₦) were presented in a transparent passion against the corresponding consequences of the therapy. The consequences of the therapy considered include; symptoms resolution (estimated as number of symptoms after therapy); AEs (mean number of pints of treatment related blood transfusions i.e., haematological AEs, increased alanine amino transferase (ALT) i.e., hepatological toxicity marker, increased creatinine i.e., renal toxicity marker); fertility preservation, and 1-year-overall survival rate (OSR).

Ethical Considerations

Ethical approvals were obtained from the Health Research Ethics Committees of UDUTH (UDUTH/HREC/2018/No.731) and ABUTH (ABUTH/HREC/CL/05) before the commencement of the data collection. Confidentiality and anonymity of patients were maintained during and after the study.

Data analysis

The data obtained were sorted, coded and entered into SPSS package V. 20 (SPSS Inc., Chicago, IL, USA) for windows and subsequently analyzed. The data were summarized as frequencies, percentages and means ± SD. Paired *t*-test was used to test for the mean difference in QALY associated with different therapy options at baseline and the 12-month follow up. One-way ANOVA was used to test for the differences in mean costs of different cost components, mean total cost and QALY per patient at the end of 12-month follow-up for the different therapy options used. The QALYs was calculated using The Complex Number Model as shown in equation 1 below:

$$QALYs = \left(\frac{\sqrt{1+U^2}}{\sqrt{2}}\right) * D \quad \text{..... Eqn. 1}^{11}$$

Where: U = 15D Utility valuation; D = Duration of study in years

The ICUR was calculated as the ration of the incremental cost to that of the utility (QALY) as shown in equation 2 below:

$$ICUR = \frac{\text{Incremental Cost}}{\text{Incremental QALY}} \quad \text{..... Eqn. 2}$$

All costs were reported in year 2019 values of Naira (₦ 380= $1). A significance level of $p< 0.05$ was used.

RESULTS

A total of 205 patients were recruited from the hospitals over the six months recruitment period. Out of this total, six patients failed the eligibility criteria, eight did not consent to participate in the study and 34 dropped out of the study due to loss on follow-up. Overall, 157 patients were available for the final analysis.

Table 1: Socio-demographic and clinical characteristics of the patients

Socio-demographic and clinical characteristics *(N = 157)*	**n (%)**
Mean Age (Years)	50.7±9.0
Mean BSA (m^2)	1.63±0.18
Marital Status, n (%)	
Single, n (%)	1 (0.6)
Married, n (%)	128 (81.5)
Divorced, n (%)	12 (7.6)
Widow, n (%)	16 (10.2)
Parity, n (%)	
Nulliparous, n (%)	1 (0.6)
Uniparous, n (%)	2 (1.3)
Multiparous, n (%)	154 (98.1)
Level of Education, n (%)	
Non Formal, n (%)	61 (38.9)
Primary, n (%)	9 (5.7)
Secondary, n (%)	54 (34.4)
Tertiary, n (%)	33 (21.0)
Occupation, n (%)	
Unemployed, n (%)	9 (5.7)
Housewife, n (%)	92 (58.5)
Business, n (%)	24 (15.3)
Civil servant, n (%)	26 (16.6)
Farmer, n (%)	3 (1.9)
Student, n (%)	3 (1.9)
Average Monthly Income, n (%)	
<₦50,000, n (%)	68 (43.3)
₦50,000-100,000, n (%)	66 (42.0)
>₦100,000, n (%)	23 (14.6)
Clinical Stage, n (%)	
I, n (%)	8 (5.1)
II, n (%)	59 (37.6)
III, n (%)	74 (47.1)
IVA, n (%)	11 (7.0)
IVB, n (%)	5 (3.2)
Histological Type (n=*156*), n (%)	
Squamous Cell Carcinoma, n (%)	144 (92.3)
Adenocarcinoma, n (%)	12 (7.7)

Socio-demographic and clinical characteristics of the patients

The mean age of the patients was 50.7±9.0 years. Most of the patients 68 (43.3%), earned an average of <₦50,000.00 per month. Majority of the patients 74 (47.1%) presented with baseline clinical stage III, while stage IVB 5 (3.2%), (p<0.001), was the least presented clinical stage at baseline. Squamous Cell Carcinoma 144 (92.3%) was the major histological type. Other details of the patients' baseline socio-demographic and characteristics of the patients can be seen in Table 1 below.

Therapy options received by the patients

A total of six therapy options including chemotherapy (CT), radiation therapy (RT), chemoradiation therapy (CRT), adjuvant chemotherapy (CTS), adjuvant radiation therapy (RTS) and adjuvant chemoradiation therapy (CRTS) were used among the 157 CC patients. A total of 78 (49.7%) patients were placed on CT, making it the main therapy option received by the patients. The specific drugs utilized for chemotherapy include Cisplatin, Cisplatin + 5FU, Cisplatin + Paclitaxel, Carboplatin + Paclitaxel and Carboplatin + Docetaxel. One patient (0.6%) was prescribed RT making it the least therapy option received by the patients. CRT, CTS, RTS, and CRTS were received by 51 (32.5%), 7 (4.5%), 4 (2.5%) and 16 (10.2%), p<0.001 patients respectively. External beam radiation therapy (EBRT) was the only form of radiation received by patients treated with radiation therapy.

Table 2 below showed that CRTS had the highest, while CT had the lowest mean total cost of therapy option per patient; ₦663,497 ($1,746) ± 164,690 ($433) and ₦356,095 ($937,095) ± 190,993 ($503), p<0.001 respectively. Patients who were treated with RTS gained the highest, while those treated with CT gained the lowest QALY per patient at the end of the 12-month follow-up; 1.0506 ± 0.01 and 0.95248 ± 0.13, p=0.001 respectively.

Cost-utility analysis (CUA)

When CRT & CTS, RTS & CT, CRT & CT, RTS & CTS and CTS & CT were compared, CTS was found to be the most cost-effective therapy option with an ICUR of ₦529,042 ($1,392) per QALY, while CRT was found to be least cost-effective therapy option with an ICUR of ₦9,511,087 ($25,029) per QALY. Interpretation of this results should be based on the consideration that, the cost of "fertility loss" due to therapy options involving surgery was not taken into consideration. See Table 3 below.

Cost-consequence analysis (CCA)

RTS had a mean total cost per patient of ₦452,009 ($1,189) ± 10,619, with the best symptoms' resolution and survival; unfortunately, fertility not preserved. CT was found to have the least mean total cost per patient (₦356,095 [$937] ± 19093) and preserved fertility; however, with least (88.5%) 1-year overall survival rate, worst complete symptoms resolution (only 20% of the patients) and mean number of pints of treatment related blood transfusions of 1.5 ± 0.7 as well as the highest patients with increased ALT (9%) (See Table 4 below).

Table 2: Mean costs of different cost components, total cost and QALY per patient at the end of 12-month follow-up for different therapy options

Mean costs and QALY per patient	*(N=157)*	Therapy options received				
	CT (M±SD)	**CRT** (M±SD)	**CTS** (M±SD)	**RTS** (M±SD)	**CRTS** (M±SD)	***P-Value***
Total cost of lab investigations (₦)	58,056±2,175	57,216±4,824	58,243±378	58,100±0000	60,188±3734	0.100
Cost of radiation therapy (₦)	N/A	178,431±82,009	N/A	250,000±0000	250,000±0000	0.003
Cost of TAH and/or BSO (₦)	N/A	N/A	55,000±0000	55,000±0000	55,000±0000	-
Total cost of drugs (cytotoxics, premeds and mgt. of AEs) (₦)	289,670±133,718	194,821±127,520	212,219±188,917	2,100±0000	208,323±164,627	0.001
Total cost of hospital and auxiliary care (₦)	28,491±7,373	77,333±32,866	30,634±8,599	88,383±11,669	89,985±12,642	<0.001
Total cost of therapy option per patient (₦)	356,095±190,993	508,880±199,148	377,627±136,504	452,009±10,619	663,497±164,690	<0.001
QALY gained	0.95248±0.13	1.0071±0.09	0.9932±0.06	1.0506±0.01	0.9935±0.09	0.001

CT=Chemotherapy, RT=Radiation Therapy, CRT=Chemoradiation Therapy, CTS=Chemotherapy and Surgery, RTS=Radiation Therapy and Surgery, CRTS= Chemoradiation Therapy and Surgery, TAH=Total Abdominal Hysterectomy, BSO=Bilateral Salpingo Oophorectomy, AEs=Adverse Events, QALY=Quality Adjusted Life Year.

Table 3: Costs-utility analysis for different therapy options at the end of 12-month follow-up

Therapy options received		Mean Cost (₦)	Mean QALY Gained	C/E	Incremental cost	Incremental QALY	ICUR (₦)
A	CRT	508,880	1.0070	505,342.60	131,253	0.0138	9,511,087
	CTS	377,627	0.9932	396,458.79			
B	CRT	508,880	1.0070	505,342.60	152,785	0.0545	2,803,394
	CT	356,095	0.9525	358,533.02			
C	RTS	452,009	1.0506	430,238.91	74,382	0.0574	1,295,854
	CTS	377,627	0.9932	396,458.79			
D	RTS	452,009	1.0506	430,238.91	95,914	0.0981	977,717
	CT	356,095	0.9525	358,533.02			
E	CTS	377,627	0.9932	396,458.79	21,532	0.0407	529,042
	CT	356,095	0.9525	358,533.02			

C/E=Cost/Effect, ICUR=Incremental Cost Utility Ratio, QALY=Quality Adjusted Life Year, CT=Chemotherapy, RT=Radiation Therapy, CRT=Chemoradiation Therapy, CTS=Chemotherapy and Surgery, RTS=Radiation Therapy and Surgery, CRTS= Chemoradiation Therapy and Surgery.

Table 4: Cost-consequences analysis for different therapy options at the end of 12-month follow-up

Therapy option received	**Mean total cost per patient (₦)**	**Consequences**								
		Symptom resolution No. symptoms after therapy, n (%)				*Adverse events*				*Survival*
						Mean No. of pint of treat. related blood transfusions	Increased ALT, n (%)	Increased creatinine, n (%)	Fertility preservation	1-Year-OSR (%)
		0.0	1.0	2.0	3.0	Mean ± SD				
CTS	377,627±136504	6 (85.7)	1 (14.3)	-	-	0.3 ± 0.8	-	-	Not preserved	100.0
CRT	508,880±199148	34 (66.7)	11 (21.6)	6(11.8)	-	1.9 ±0.6	1 (4.8)	2 (8.7)	Preserved	92.2
CT	356,095±19093	16 (20.5)	21 (26.9)	28 (35.9)	13 (16.7)	1.5 ± 0.7	4 (8.7)	-	Preserved	88.5
RTS	452,009±10619	4 (100.0)	-	-	-	-	-	-	Not preserved	100.0
CRTS	663,497±164690	14 (87.5)	2 (12.5)	-	-	1.0 ± 0.5	-	-	Not preserved	100.0

No. of symptoms after therapy: 0.0=no symptom (complete resolution), 1.0= PVB or PVD, or LAP, 2.0=PVB and PVD or LAP, or PVD and LAP, 3.0= PVB, PVD and LAP, CT=Chemotherapy, RT=Radiation Therapy, CRT=Chemoradiation Therapy, CTS=Chemotherapy and Surgery, RTS=Radiation Therapy and Surgery, CRTS= Chemoradiation Therapy and Surgery, ALT=Alanine Amino Transferase, AST=Aspartame Amino Transferase, OSR=Overall Survival Rate.

DISCUSSION

This study was conducted to evaluate the cost-utility and cost-consequence analysis of different CC therapies received by patients in two Nigerian tertiary hospitals. The availability of radiation therapy was hampered by radiotherapy machines defaults (breakdown) especially in ABUTH study center. Hence, some patients in UDUTH center were opportune to receive the guidelines recommended, while others in both centers received CT or CTS as the only available therapy options. Thus, this study compared the guidelines recommended therapy options with available therapy options (as alternatives) received by the patients in the study centers.

It was observed that, when CRT & CTS, RTS & CT, CRT & CT, RTS & CTS, and CTS & CT were compared, CTS was found to be the most cost-effective therapy option while CRT was found to be least cost-effective therapy option. Interpretation of this results should be based on the consideration that; only direct medical costs were used as information on other costs including cost of "fertility loss" due to therapy options involving surgery were not available. A cost-effectiveness analysis study showed cisplatin + paclitaxel as an acceptable alternative to cisplatin alone for the treatment of advanced or recurrent CC patients, and that the addition of topotecan did not increase survival enough to justify the increased cost[4].

Similarly, a cost-effectiveness model developed using data from the UK fluorouracil, oxaliplatin and CPT11 (irinotecan) use and sequencing (FOCUS) trial, showed that the combination of 5FU and irinotecan (whether used first or second line) appears to be more cost-effective than the single agent sequential therapies used in the FOCUS trial or 5FU plus oxaliplatin[5]. A study conducted to examine the value for expenditure between radical hysterectomy with pelvic lymph node dissection (RHPLND) with or without postoperative adjuvant therapy and concurrent chemoradiotherapy (CCRT) in patients with stage IB cervical cancer showed RHPLND as the most cost-effective therapy option[6].

In this study, when the total mean costs of therapy per patient were presented against the corresponding consequences (symptoms' resolution, adverse events and survival) of the different therapy options, RTS was found to costs high with the best symptoms' resolution and survival, unfortunately, fertility not preserved. CT was found to have the least mean total cost and preserved fertility; however, it was associated with the least 1-year OSR, worst symptoms resolution, considerable haematological and hepatological AEs. Studies evaluating the cost-consequences analysis of CC therapies are lacking. In a cost-consequences analysis study of endometrial cancer, patient incurred higher costs associated with relatively heavy use of a wide variety of different resources against the consequences of relapse[12]. Another study showed that, blue light cystoscopy (BLC) with hexaminolevulinate (HAL) decreases disease recurrence in patients with non-muscle-invasive bladder cancer (NMIBC), with a five-year cost of approximately $1–5 million for jurisdictions of 4–13 million people[13]. Of interest to healthcare administrators, this also reduces the bed-day requirement of patients undergoing transurethral resection of bladder tumour (TURBT), allowing redistribution of hospital resources, including the treatment of more patients[13].

Limitations of the Study

One of the major limitations to this study is its observational nature because, the potential for bias is higher in observational studies. However, the use of instrumental variables analysis which is one of the methods employed to improve causal inference from observational research have addressed some of these concerns although not completely eliminate them[14].

The availability of radiation therapy was hampered by radiotherapy machines defaults (breakdown) especially in ABUTH study center. Hence, some patients in UDUTH center were opportune to receive the guidelines recommended, while others in both centers received CT or CTS as the only available therapy options.

CONCLUSION

Adjuvant chemotherapy (CTS) was found to be the most cost-effective therapy option, while CRT was found to be least cost-effective therapy option received by the patients. Adjuvant radiotherapy (RTS) had a moderate mean total cost per patient with the best symptoms' resolution and survival; unfortunately, fertility not preserved. Healthcare providers should discuss the economic implications of different therapy options with the patients including their consequences, to enable them to direct their economic efforts and expectations based on their economic capacities.

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