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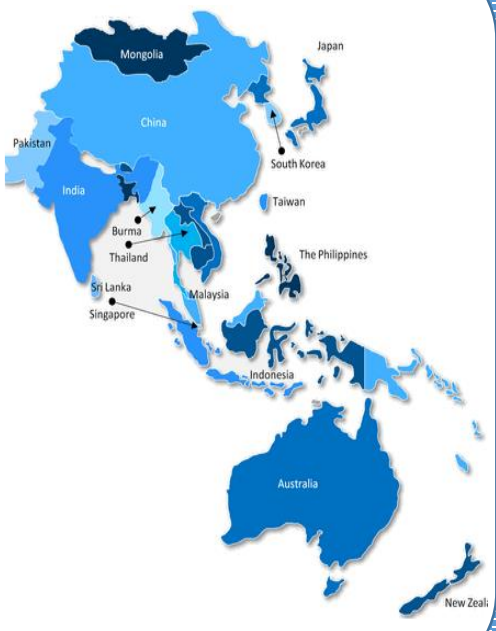

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RESEARCH ARTICLE

Cancer Patients' Perspectives on Integrating Cancer Care in Primary Care Settings: A Qualitative Inquiry

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Abstract

Introduction: Research has demonstrated the importance of general practitioners in providing care for cancer patients within the concept of 'care closer to home'. This study reports cancer patients' views and expectations on integrated cancer care in primary care settings in Brunei. **Methods:** A qualitative approach using semi-structured in-depth interviews with cancer patients were conducted. The interviews were recorded, transcribed, and analysed using thematic analysis. **Results:** 13 cancer patients participated and were interviewed, leading to three key themes that emerged from this study: (i) perceived challenges for providing cancer care at primary care settings; (ii) current health care system favours hospital-based cancer care and (iii) expectations towards integration of cancer care into primary care. **Conclusion:** Participants expressed their acceptance to the concept of primary care-based cancer care, mainly due to convenience and minimised waiting time. For this to be in place, there is a need for stronger communication channels between general practitioners and hospital physicians, familiarity of patients' cases among general practitioners, in-depth knowledge and experience of general practitioners in cancer care, and consulting the same general practitioners to provide continuity of care.

Keywords: Cancer care- patients' perspectives- integration- primary care- qualitative

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Introduction

Globally, there is an increase in newly diagnosed cancer patients and cancer survivors as a result of growing and aging population, and technological advances in cancer care [1-2]. Conventional hospital based cancer care causes a significant burden on tertiary care, yet it is unclear whether it provides early diagnosis of recurrence and improve survival [3]. Meanwhile, primary care is increasingly promoted by governments worldwide as the preferred place for cancer care, due to health care costs and patients' preferences [4]. Evidence is emerging that there are no differences in cancer patients' overall well-being, recurrence rates, survival between primary and hospital-based follow up, with primary care found to be more cost-effective [5-6].

Integrated cancer care between primary and tertiary care settings is recently evidenced as a successful model of care. Indeed, integrated follow up in primary care for people with breast and colorectal cancers showed high patient satisfaction and no adverse outcomes [7-8]. A study assessing general practitioners' (GP) attitudes toward follow-up after cancer treatment showed that they felt confident in doing so and would like to contribute to long-term care of cancer patients [9]. Meanwhile, patients had also reported their views for greater involvement of GPs in all aspects of their cancer care [10] and cancer survivors had shown satisfaction with primary care delivery [11]. It has been predicted that integrated cancer care may save up to 75% of health care costs [12].

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In Brunei, cancer has been the leading cause of mortality from 2009 to 2017, with 19.3% of deaths in 2017 [13]. At this stage, cancer patients' expectations on integrating cancer care into local primary care settings are not yet known. This study reports cancer patients' experiences, preferences, and expectations towards the integration of cancer care in primary care in Brunei.

Materials and Methods

Design, Setting and Participants

We adopted a qualitative approach and considered that semi-structured in-depth interviews with cancer patients were the most appropriate research technique to capture our research aims. Cancer patients aged between 18 and 80 years old attending the oncology outpatient clinic in the main hospital in Brunei undergoing either active treatment, palliative care, or in remission, were included in the study. Following ethical approval, nurses working in the oncology clinic approached eligible patients. Patients who agreed to participate were given a participant information sheet and further explanation about the study by the main researcher (SMC) and were interviewed at an agreed date, time and location.

Data Collection

Semi-structured in-depth interviews were conducted between February to November 2017 with thirteen participants. An interview guide (Table 1) derived from literature review and consensus of research team was developed with a view to obtain participants' experiences, views and expectations towards their cancer care in primary care. We operationally defined cancer care as care provided when patients were receiving diagnosis, referral, active treatment, palliative care and related follow-up care in cancer.

SMC, the main researcher, was guided by a senior investigator (MRV), with vast experience in conducting and analysing interviews on cancer-sensitive topics. The interviews lasted between 22 to 60 minutes and were conducted in private rooms at various places - health centres, oncology clinic, the university where the researchers were based, participants' home and participants' workplace as per mutually agreed. As the questions asked may be sensitive to participants, necessary steps were taken to ensure that participants felt comfortable and were reassured about confidentiality and anonymity. All forms of communication with participants were conducted in a supportive way and appropriate empathic responses were used to acknowledge their distress. We followed the principles of qualitative research [14] and ended further interviews when data saturation was reached at the 13th interview.

Data Analysis

The interviews were digitally recorded, transcribed verbatim, and analysed using thematic analysis [15]. Firstly, the transcripts were read to get an immersion into the interview data. Subsequently, initial codes were developed; the coded units which represented the different aspects of participants' experiences, preferences, and expectations towards integration of cancer care in primary care settings were identified. The coded data was compiled under wider subthemes, which were compared to the original transcripts for consistency and contextual verification. Consequently, the contents in each subtheme were summarised, which generalised the descriptions concerning the research topic. SMC and MRV coded the data together and agreed on the final themes. An audit trial was performed by SMC and MRV to enhance trustworthiness of the study.

Ethical Considerations

The study was approved by the Ministry of Health Research and Ethics Committee and Ethics committee of PAPRSB Institute of Health, Universiti Brunei Darussalam (UBD/IHS/B3/8).

Results

The general characteristics of the participants are shown in Table 2. There were ten females and three males of median age 50 years. The most prevalent cancers were lung and breast. Most were diagnosed with cancer within the last 5 years.

Data analysis led to three main themes of participants' range of perspectives on primary care-based cancer care: (i) perceived challenges for providing cancer care at primary care settings, (ii) current health care system favours hospital-based cancer care and (iii) expectations towards integration of cancer care into primary care, further explained below.

Theme 1: Perceived challenges for providing cancer care at primary care settings

Most participants regarded cancer as a specialised area requiring specialist knowledge, thus their care would be most appropriately followed up in a hospital setting than in primary care. Participant 6 questioned the ability of cancer care at the primary care, as described below:

'Hospital has specialist for cancer. For my case, I am categorised as severe, so if I go to the hospital, then I would be handled with the proper care because hospital is specific for cancer.' (P6)

A few participants felt that hospital physicians would do more thorough investigations instead of the GP, as questioned by Participant 10:

'Why does specialist do all sorts of investigations but the normal doctor in clinic does not?' (P10)

A few participants presented to the GP repeatedly with the same complaint. However, the symptoms of cancer were disregarded by the GPs and participants did not agree with the diagnosis, as illustrated by Participant 13:

'They (GPs) examined my abdomen. They just pressed like that. They just said it was gastric….. I mean they should check thoroughly. They should focus on where exactly the pain is. They (GPs) just gave me reflux medication. After two to three weeks, I would go to the health centre again. Same problem. It was always the same. They did nothing.' (P13)

Table 1. Interview Guide

Interview guide	Questions
Experiences	·How were you diagnosed with cancer?
	·When did you last see the GP regarding your concerns related to cancer?
	·Were there any problems in seeing the GP regarding your cancer?
Views	·Do you think the GP can detect your cancer early?
	·How do you think the GP can be involved in your care?
	·Do you think the GP can look after cancer patients? Are there challenges in this?
	·Would you like the GP to know if you are admitted in hospital? How could this information help?
	·How can hospital doctors and GPs work together to help cancer patients?
Expectations	·Are there any areas where you would like your case to be taken over by the GP rather than the hospital?
	·What kinds of support would be most useful/beneficial for you and other patients with cancer, which can be provided by primary care?

Participants also reported that the GPs lacked knowledge and skills of managing cancer. As a result, they felt that follow up in the hospital setting would be more ideal, as illustrated by Participant 11:

'When one goes to the area clinic, I am afraid the doctor does not know the story even though there is Bru-HIMS (unique patient electronic medical record number). One will not feel comfortable, needing to tell again what happened.' (P11)

On the other hand, we also found overall positive experiences from participants who were satisfied with the services provided in the primary care. Participant 7 stated that she was referred promptly to the hospital for further evaluation of the possibility of cancer:

'At first I had fever. So, I went to 'X' Health Centre. The doctor requested for blood tests. From there, it was found and I was sent straight to the hospital for further evaluation.' (P7)

Some participants agreed that utilising primary care would reduce patient load at acute hospital. Participant 7 reported that cancer care at primary care settings would provide more choice of doctors than a specialist doctor at acute hospital, hence, cancer care should be 'delegated.'

'Don't rely only on one doctor - I sympathise. The patients are a lot (in hospital). So, if possible, the tasks can be delegated.' (P7)

Most of the participants reported the benefits of a primary care-based cancer care would include care closer to home, convenience, availability of doctors, and less waiting time.

'The doctors are always there (in health centres). Waiting time is not too long. It is good. I just register and pay a dollar and waiting time to see the doctor is not long.' (P12).

Theme 2: Current health care system favours hospital-based cancer care

Participants reported that current cancer care pathway mainly favours hospitals than primary care. Currently in Brunei, patients who were referred from primary care for further evaluation of possibility of cancer diagnosis would continue to be cared for by the hospital physician from diagnosis, treatment, and surveillance phases. This lead to cancer patients approaching the hospital physicians only for any cancer-related issues instead of their GPs who were not engaged in any aspects of their cancer care, as mentioned by Participant 2:

'Since I was diagnosed with cancer, I have only been going to the main hospital. I have not been to the health centre.' (P2)

Some preferred a hospital-based cancer care pathway as they felt more comfortable talking to the same physicians whom they were already familiar with since their cancer diagnosis.

'Mostly patients feel comfortable with the doctors in the main hospital. They will prefer to go to hospital only.' (P11)

Participants also reported other system errors such as the availability of cancer medications only in tertiary hospital, and inflexible and rigid working hours of primary care confined to the normal working hours. These system factors favoured more towards hospital settings to provide cancer care, as illustrated by Participants 2 and 9:

'Well, I just go straight to hospital because they have emergency in hospital. And the health centre here, it is only opened during office hours.' (P2)

'There is an issue if I collect my medication here (health centre), as my cancer medication is not available here. I will need to go to hospital.' (P9)

Theme 3: Expectations towards integration of cancer care into primary care

It was clear in most participants' discussions that they were open to the concept of primary care-based cancer care, and that cancer care should not be based only in the hospital setting. Indeed, participants suggested possible ways for integration between primary and secondary care. For example, participant 4 commented on 'oncologist coming to the health centre'. Apart from that, participant 12 felt that 'there should be constant communication between GPs and hospital physicians'.

Participant 10 reported that she would prefer to see the hospital physician occasionally still while GPs could do the more regular routine follow up. In order for this to take place, both doctors from the primary and secondary care should be working together.

Table 2. General Characteristics of Study Participants

Participant	Sex	Age	Profession	Education	Year of cancer diagnosis	Location of cancer	Treatment
P1	F	35	Housewife	High school	2009	Brain	Surgery, radiotherapy
P2	M	40	Police	High school	2014	Colorectal	Surgery, radiotherapy, chemotherapy
P3	M	62	Retired	University	2009	Lung	Radiotherapy, chemotherapy
P4	F	67	Retired	High school	2016	Lung	Chemotherapy
P5	F	63	Housewife	High school	2008	Lymphoma	Chemotherapy
P6	F	47	Self-employed	Primary school	2009	Breast	Surgery, hormonal therapy
P7	F	50	Teacher	University	2013	Rectal	Surgery, chemotherapy
P8	F	55	Housewife	High school	2016	Lung	Patient refused treatment
P9	F	68	Housewife	High school	2016	Breast	Hormonal therapy
P10	F	51	Operator	High school	2000, 2014	Thyroid, liver	Surgery, radiotherapy, chemotherapy
P11	F	48	Dental nurse	University	2014	Breast	Surgery, chemotherapy
P12	M	26	Officer	High school	2016	Brain	Radiotherapy, chemotherapy
P13	F	42	Cleaner	High school	2014	Liver	Surgery

'It is ok (for cancer care in the community). Like I said, as long as there is a connection with Dr 'X' (hospital physician). Once in a while, patient can still see Dr 'X'. Not every 1-3 months, but once in a while. Still it is important to see him. He is like the director of the movie. But for the routine appointments, we can see the GPs.' (P10)

As of now, patients in primary care settings may not necessarily see the same GPs, which may lead to unfamiliarity of cases and needing the patients to explain what had happened, as commented by Participant 10:

'Sometimes doctors (GPs) do not check the files thoroughly. So, I have to explain everything from A to Z again. So, it is better for me to go to my own doctor (in hospital).' (P10)

In order to overcome this issue, there has been a suggestion of 'seeing the same doctor' in primary care so to avoid confusion as different doctors would have different approaches to management plans, as illustrated by Participant 13:

'When we see the doctor, he will say this. For the review appointment, a different doctor will say different things. So which advice do we follow? We don't know. We are just following doctor's advice. If possible, it would be better with the same doctor.' (P13)

Discussion

Many existing studies on primary-based cancer care have reported cancer patients' attitudes, health behaviours, preferences and perspectives [16-19], whereas our study focused on cancer patients' experiences and expectations towards integrated cancer care in primary care.

Firstly, inconsistent assessment and diagnostic procedures among GPs seems to frustrate cancer patients, hence leading to multiple visits to primary care. The National Cancer Diagnosis Audit in the United Kingdom showed that 26% of patients had three or more GP consultations before being referred to hospital care for further evaluation [20]. Lyratzopoulos et al. [21] showed that some patients experienced multiple consultations leading to prolong intervals to specialist referral and assessment for suspected cancer. Mendonca et al. [22] also reported 40% of patients who had multiple GP consultations were not satisfied with how hospital physicians and GPs collaborate. Cancer diagnosis remains challenging in primary care as cancer patients present to GPs without any cancer alarming symptoms as shown in a study by Jensen et al. [23]. In the United Kingdom, cancer care two-week wait referral pathways aim to improve patients' satisfaction, reduce waiting times to be seen by specialists, and earlier diagnosis, which would result in better prognosis of patients [24]. Yet, there is no evidence available on development and test of integrated cancer care pathway for assessment, diagnosis and referral of suspected cancer.

Misperceptions about primary care-based cancer care as an avenue for 'minor illness' management among cancer patients often limit integration of cancer care in primary care settings [25]. Our study participants believed that their cancer care would require a specialists' expertise of cancer, of which GPs do not acquire. Hence, they reported their refusal to visit primary care as the GPs would still refer them to hospital eventually, similar to a Danish study [26]. Patients expressed strong preferences for quick diagnostic evaluation after initial presentation to GPs and would choose to undergo investigations for suspected cancer even if their risk was as low as 1% [27]. In contrast, GPs in other studies reported that they valued their role as gatekeeper and perceived their skills as being able to identify patients who needed further work up and referral to hospital from those who were able to manage in primary care [28]. Public awareness interventions on role of GPs in cancer care may challenge such misperceptions.

In view of the increasing cancer survival rates, managing cancer patients in the primary care has been identified as a key element for future-effective and cost-effective cancer care [29]. Participants reported that cancer care tasks from hospital could be delegated to primary care. Indeed, the roles of primary care-based cancer care are also widely accepted by cancer survivors, similar to many studies [5]. Participants also reported care closer to home, and easy accessibility of GPs, as advantages of integrated cancer care in primary care [4-

30]. Yet, lack of cancer diagnostic skills, limited education, knowledge and skills, experience, and available time of GPs were perceived barriers by patients for primary-based cancer care [26]. Mao et al. reported that half of the patients with breast cancers had concerns about GPs' ability to address patients' cancer-specific issues [31]. In another qualitative study, cancer patients did not see their GPs, because they felt that the GPs were too busy or to be lacking in oncology knowledge [32].

In the current tertiary-based cancer care centre in Brunei, similar to many countries, cancer patients seem to lose their follow up by GPs [33]. Another possible explanation may be because in developing countries, cancer patients are still traditionally followed up in hospital setting, as compared to developed countries, whereby there is already a gradual shift of cancer care from secondary to primary care settings [34]. Patients in our studies, similar to other studies, prefer doctors whom they are most familiar with, and who oversaw them during their active cancer treatment [35]. This could be due to the strong relationship built between the patients and hospital physicians during patients' active treatment [31-32]. Therefore, the current structure of cancer care has led our participants to approach the hospital for their cancer care instead of attending primary care.

In contrast, other studies reported that patients who were already receiving cancer follow-up from their GPs were satisfied with the care provided and did not report any drawbacks [25-31]. For example, Nyarko et al. [11] reported high satisfaction rates on primary care delivery among cancer survivors. Hence, integrated pathways should empower earlier involvement of GPs during the active cancer treatment stage that may increase patients' confidence in primary care-based follow-up. The participants in our study also discussed about the inflexibility of opening hours of primary care. Similarly, many patients also felt that it was difficult to approach GPs after office hours [36]. In fact, a study by Borgsteede et al. [37] reported the main factor for effective out of hours cancer care is the accessibility of GPs and nursing support.

Our study provided evidence for participants' acceptance towards integrated cancer care at primary care settings, conditional in having clear roles and responsibilities of GPs and hospital physicians, effective communication between GPs and hospital physicians, guidance on follow-up protocols and common treatments, knowledgeable GPs in cancer care and rapid access to specialists [26]. Indeed, such integrated care with GPs and hospital physicians show no adverse outcomes in patients with bowel and breast cancers and can provide high patient satisfaction rates [7-8]. On the other hand, our study also showed that GPs were unfamiliar with their cases leading to poor satisfaction and frustration among cancer patients in primary care. This is similar to studies by Thind et al. [25] and Roorda et al. [26], which reported lack of GPs' knowledge on patients' histories was regarded as a disadvantage.

To overcome such inconsistent approach, patients valued and preferred to be followed up by the same care provider at each visit because of the established doctor-patient relationship as well as physicians' knowledge and familiarity on the patients' histories [33-35]. Seeing the same GPs would also cause less confusion in management plans and also remain as effective way of securing good information, thus enable GPs to provide seamless care along the entire cancer care spectrum [38]. Continuity of cancer care would result in better communication, stronger relationship between GPs and patients, allow patients to cope better, enhance patient access to care, and improve overall experiences for cancer patients [39].

This study was not without limitations. Firstly, as many had their cancer diagnosis more than 5 years ago, there may be recall bias as information provided was relied on what participants reported and might had affected the accuracy of recalling the actual experiences. Secondly, the interviewer was a GP who may influence the participants' views, despite our reassurance.

In conclusion, this study adds to the growing existing evidence base looking at factors and barriers of integrating cancer care in primary care. We found that our cancer patients were receptive to the idea for cancer care to be integrated in primary care. However, in order for this to take place, it is important to ensure established communication channels between GPs and hospital physicians, deeper understanding of cancer cases among GPs, improved cancer care knowledge and experience of GPs, and consulting the same GPs to provide continuity of care, as factors that enable quality cancer care at primary care settings in Brunei. Thus, policy makers should incorporate these elements of integration in the implementation of cancer care into primary care, especially for Brunei before we are ready to integrate a primary care cancer care. Furthermore, future research needs to address GPs' knowledge gaps in cancer care and to explore development and test of integrated cancer care pathways in primary care settings.

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RESEARCH ARTICLE

Knowledge and Attitudes of Nursing Students Towards Smokeless Tobacco and Areca Nut Control in Central Province of Sri Lanka

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Abstract

Background: Use of smokeless tobacco (SLT) and areca nut (AN) is widespread in Sri Lanka. Several workshops to train healthcare workers on SLT/ AN cessation programmes (SLT/AN-CP) were carried out. Objective of the study was to evaluate the enhancement of knowledge and attitudes related to SLT/AN-CP among nursing students following a workshop. **Methods:** A cross sectional study was conducted with the use of two questionnaires. A total of 212 nursing students were assessed and the study group included 184 females (86.8%). **Results:** Results were analyzed according to the 3 main areas of the assessment, i.e knowledge related to Oral cancer, knowledge related to SLT, its effects and cessation practices and attitudes regarding SLT cessation counselling. Out of the eight questions to assess the knowledge related to oral cancer, five questions demonstrated a statistically significant difference ($P<0.05$) following the workshop when compared to the pre workshop knowledge. Even though, majority had a good knowledge on harmful effects of SLT and AN, it was interesting to note that 14.15 % of the participants were unaware about the fact that the oral cancer is the commonest cancer among Sri Lankan males. 96.7% agreed that proper counseling would lead patient to quit the habit. **Conclusions:** This preliminary study showed that the knowledge and attitude towards SLT/AN-CP among nursing students were satisfactory and effective workshops can be used to improve their knowledge and attitudes towards SLT/AN-CP especially in low economical settings.

Keywords: Smokeless tobacco- arecanut- tobacco cessation- nursing students

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Introduction

Tobacco is one of the greatest threats to global health today. Use of both smoking and smokeless tobacco (SLT) is associated with increased risk of chronic and terminal diseases. These encompass periodontal diseases, oral and pharyngeal cancers, myocardial infarction, stroke, erectile dysfunction and problems in pregnancy, leading to stillbirths and low birth weight babies [1]. SLT is an addiction for millions of people worldwide, and research indicates that the use by young individuals in many countries is increasing. The magnitude of this problem in Sri Lanka was showed in a recent survey, where 15.8% of Sri Lankans which includes 8.6% of the youth have been estimated to be smokeless tobacco (SLT) users [2]. SLT users outnumber the estimated number of smokers in many countries of the region including Sri Lanka; the prevalence of smoking is decreasing, while the use of SLT is on the rise [3]. A variety of types of SLT are consumed throughout the world and these include betel

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quid and other commercially available tobacco products such as pan masala, mawa, red tooth powder, khaini, tobacco powder, zarda and many more [2].

The harmful effects of SLT use has been well documented and includes oral squamous cell carcinoma (OSCC) at the dubious first place producing the highest incidence and highest mortality out of all cancers among Sri Lankan males [4]. However, it is unfortunate that successful SLT cessation remains a weak point in tobacco control in the South-East Asia Region. Though there is clear scientific evidence that tobacco cessation interventions are highly cost-effective public health measures, countries of the region have failed to optimally prioritize this issue so far and therefore, programmes are yet to be developed to eradicate this preventable menace [5-6].

Majority of patients with OSCC is preceded by oral potentially malignant disorders (OPMD) [5-8]. According to the management protocols of OPMD established in Sri Lanka [9] low risk OPMDs are managed at primary care level by general dental practitioners with education on habit intervention with 6 month review appointments. Thus, Dental professionals are well suited and can play a major role in tobacco cessation activity [10-13]. However, the National Institute for Health and Care Excellence (NICE) (2012) guideline for Smokeless tobacco recommends the involvement of primary and secondary dental care teams (example, dentists, dental nurses and dental hygienists) for providing brief advice and referral in South Asian communities [14]. Therefore, in par with these professionals other than the dentists, nursing officers can play an important role in tobacco cessation (TC) activities. Majority of tobacco cessation protocols have been developed with smoking cessation in mind [15-16]. However, though the same protocols can be applied for SLT cessation as well, successful implementation may require at least some modifications. Firstly, with reference to SLT, in addition to tobacco, cessation of areca nut use should also be targeted. Furthermore, dependency and withdrawal symptoms of SLT use as well as areca nut use show differences when compared with smoking [17-18]. Thus, a training programme on SLT cessation was developed to improve the knowledge of healthcare workers with reference to above mentioned facts.

Therefore, the objective of the present study was to assess the knowledge and attitudes of nursing students in relation to SLT/AN cessation and to assess the enhancement of knowledge, and attitudes following a programme on SLT/AN cessation.

Materials and Methods

Description of the workshops conducted for SLT / AN cessation (SLT / AN cessation programmes (SLT/AN-CP)

Island-wide workshops to train healthcare workers including nursing students on tobacco cessation activities were planned in collaboration with Centre for Research in Oral cancer, Presidential task force for Drug Prevention and National Cancer Control Programme. This programme included 2 workshops conducted for nursing students from the Central Province. The workshop was conducted for a half a day, and the resource personals were subject specialists with experience in tobacco and AN cessation.

Methodology

Following the ethical approval from the Ethics Review Committee of the Faulty of Dental Sciences, a cross sectional study was conducted among the nursing students in the Central province who participated in the workshop. Two self administered questionnaires were developed by the investigators, to evaluate the nursing officers' knowledge and attitudes towards tobacco cessation practices and oral cancer. The first questionnaire which was administered prior to the workshop consisted of four components and the summary of the questioner is given in Table 1.

Self administered questinnaire was developed in Sinhala language, forward and backward translations was done in to English and Tamil languages. Content validation for this questionnaire was carried out with the help of three Consultants in Community Dentistry. The content validity ratio per item was calculated and each item in the questionnaire had a CVR ratio (CVR) of > 0.75 [8]. Pre-testing of questionnaire was conducted among ten nursing students from the Faculty of Dental Sciences, University of Peradeniya. The questionnaire was self administered on voluntary basis prior to the commencement of the workshop.

The second questionnaire contained all the components mentioned in Table 1 except the demographic profile of the patients and this was administered following completion of the workshop.

Statistical analysis

The SPSS (version 22) software package was used for the data analysis. Data obtained from the questionnaire were entered in SPSS software were expressed as frequencies (percentages) using descriptive statistics. The improvement of the knowledge following the workshop was assessed by comparing the pre vs. post workshop responses using McNemar test. Attitudinal questions were weighted and amalgamated to produce total attitudinal value for each subjects. Total values were converted to Z scores and dichotomized to unsatisfactory and satisfactory attitude. Pre and post dichotomized values were tested for significance by McNemar test. P-values of less than 0.05 were considered statistically significant.

Results

Participants who answered all items of the questionnaire were considered as complete responders and only completed questionnaires were analyzed. Out of the 212 nursing students who responded, 93 were undergraduates from the Faculty of Allied Health Sciences (AHS) and 119 was from the Nurses Training School (NTS), Kandy. The study group had a female preponderance with 184 females (86.8%) and 28 males (13.2%). The undergraduates from the Faculty of AHS

Table 1. Summary of the Pre Workshop Questionnaire

Components	No of Questions	Type of the questions
1. Demographic profile of the participants (No data was collected on personal identifiers of the students)	07	Majority dichomatous questions with Some open ended
2. Awareness and knowledge related to oral cancer	08	3-point Likert scale (true, false, and Don't know)
3. Knowledge related to smokeless tobacco, its effects and cessation practices	10	3-point Likert scale (true, false, and Don't know)
4. Attitudes regarding smokeless tobacco cessation counseling (TCC) and ways to reduce SLT use.	05	Dichotomous questions

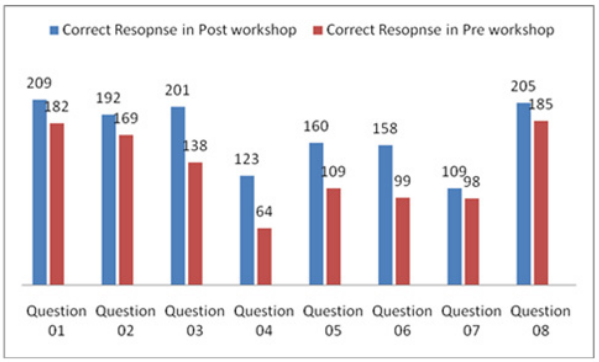

Figure 1. Graphical Representation of Participants who Indicated Correct Response to Each Question Allocated to Assess the "Awareness and Knowledge Related to Oral Cancer"

was within the age range of 20-25 years, however, the students age of NTS ranged from 20 to 50 years with 78.99% of the students of the NTS were in the age range of 20-25 years. The majority (66%) of the participants were in their 3rd year of the study programme. Only 23 (10.8%) nursing students has received training on SLT/AN cessation before coming to the workshop and out of that 23, 2.4% were in the opinion that the training they have received was adequate. Students who had a family history of oral cancer or had any immediate family member been diagnosed to have a disease (other than oral cancer) related to tobacco use was 1.9% and 4.7% respectively.

Analysis of the Awareness and knowledge related to oral cancer

Out of the eight questions to assess the knowledge related to oral cancer, five questions demonstrated a statistically significant difference ($P<0.05$) following the workshop when compared to the pre workshop knowledge. 14.15 % of the participants were unaware of the fact that Oral cancer is the commonest cancer among Sri Lankan males. However, the knowledge was drastically improved with 98.58% acknowledged this fact immediately following the workshop and the results were statistically significant at a P value of 0.00 ($P<0.05$). Further, 34.9% did not know that a longstanding white patch can be an oral cancer. It was noted that more than half of the participants, lack the knowledge on certain misconceptions such as oral cancer may occur due to spicy foods, oral cancer in the initial stages are painful and that all oral potentially malignant disorders invariably transform in to oral cancer were 68.9%, 53.3% and 53.8% respectively. They did not have a clear knowledge about the above mentioned facts and the number of correct answers received for these questions were statistically significant at a P value of 0.002, 0.004 and 0.00.

Out of the 212 nursing students who participated, 46

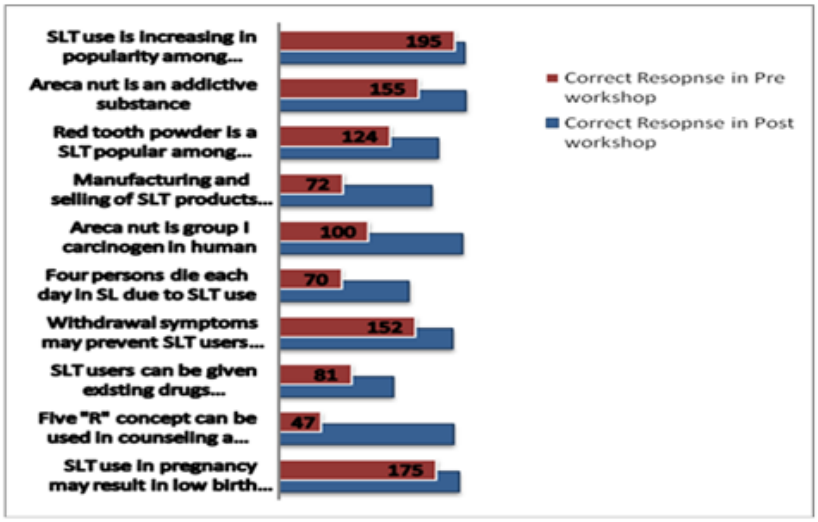

Figure 2. Graphical Representation of Participants who Indicated Correct Response to each Question Allocated to Assess the "Knowledge Related to Smokeless Tobacco, Its Effects and Cessation Practices"

Table 2. Depicts the Pre and Post Dichotomized Attitude Scores

Pre test	Post test
	Satisfactory attitudes N (%)
Satisfactory attitudes N (%)	193 (98)
Unsatisfactory attitude N (%)	4 (2)
Total N (%)	197 (100)

N- Number of questioners

(21.7%) were on the opinion that majority of oral cancers cannot be prevented and the post workshop questionnaire showed a change in this opinion with 192 participants (90.6%) stating that the statement as true with a P value of 0.092 which was not statistically significant. However, it was interesting to note that 87.3% knew that, oral cancer is curable if detected at the early stages.

Analysis of knowledge related to smokeless tobacco, its effects and cessation practices

As per the data obtained on the ten Likert scale questions, only four questions demonstrated a statistically significant difference (P<0.05). 195 (92%) agreed upon the fact that SLT use is increasing in popularity among youth and adolescents, and 124 (58.5%) were aware on the fact that "Red tooth powder" is a SLT product popular among children. This is an encouraging finding as these figures indicate public awareness. However, we found that only 155 participants (73.1%) knew that "areca nut is an addictive substance" and the correct response between the two groups (pre and post workshop) were significantly different (P =0.021; P<0.05). Further, it was also noted that only 72 (33.9%) participants were aware of the fact that "manufacturing and selling of SLT products is banned in Sri Lanka" with a P value of 0.00.

Further, majority 59.9% of the nursing students did not know the fact that "four persons die each day in Sri Lanka due to SLT use". Also, 73.1% and 51.9% respectively did not know that "SLT users can be given existing drugs prescribed to combat cigarette craving" and "Five "R" concept can be used in counseling a client who is unwilling to quit SLT use". Responses to 14 individual Likert scale items of the questionnaire have been depicted in Figure 2.

Analysis of the attitudes regarding smokeless tobacco cessation counseling (TCC) and ways to reduce SLT use

Out of the 212 participants only 197 has completely answered the section pertaining to attitudes, therefore, only those were considered for the assessment. The majority was in agreement that TCC is not effective due to lack of formal training (79.7%) and that TCC should be part of the regular treatment modalities (92.5%) and 96.7% believed that proper counseling would lead patient to quit the habit. Further, 89.1% was in agreement that the tax on tobacco products need to be increased as a measure to reduce the SLT use.

Although the attitude change is a slow process, we have attempted to analyze the Likert scale attitudinal questions by converting to the dichotomized total Z scores. Total Z score were dichotomized: Less than zero as 'unsatisfactory attitudes' and above zero as 'satisfactory' attitude. However, pre assessment among the Nursing students was revealed that only 4 students were categorized as unsatisfactory attitudes and in the post assessment no one labeled as unsatisfactory attitudes (Table 2). Therefore, there is no significant difference between pre and post assessment.

Discussion

Tobacco cessation programmes are a "need of the hour" considering the widespread use and harmful effects of tobacco. However, most of the time emphasis is given for smoking cessation, reducing the significance of smokeless tobacco / areca nut (SLT/AN) use. Though it is accepted that both practices are harmful and thus the cessation programmes for both are equally important, novel strategies are required to overcome barriers and successfully implement such programmes. This is especially true for SLT/AN, as its use is traditionally ingrained in Sri Lankan and South Asian culture. Though, at a glance one would feel that time and energy spent on SLT/AN cessation programmes by healthcare professionals are not cost effective in terms of outcome, they do have a responsibility to find strategies to overcome the negativity. Thus the idea of conducting a series of workshops to enhance the knowledge of oral cancer and SLT/AN cessation practices among healthcare professionals was initiated.

The fact that nursing officers come in contact with a high numbers of patients make them ideal to deliver SLT/AN cessation counseling. However, it was found that tobacco cessation is not an integral component of their curricula. Hence it was essential to improve their knowledge and attitudes, related to SLT/AN cessation which was attempted with the present workshop. Results of the present study revealed a significant improvement in awareness of oral cancer as well as SLT/AN cessation strategies of the participants (Figure 1 and 2) and thus workshops of this nature could be considered a cost effective method to improve awareness.

Nurses as part of healthcare professionals are in a position to educate patients regarding clinical presentations of oral cancer/OPMD, which may result in increased awareness among patients leading to early detection. The present study revealed that the nursing students were unaware of the main clinical presentations of oral cancer initially, with a significant improvement in post workshop knowledge. However, without creating an environment where this knowledge can be applied, the retention will be low as indicated by Wardh et al., (2008) [19]. In addition, though, the present study mainly focused on nursing students, it is possible to introduce such awareness programmes in the form of continuous professional development programmes to nursing officers currently working in hospitals, with the aim of recruiting them for the task of delivering tobacco cessation counseling.

Though, "manufacturing and selling of SLT products

are banned in Sri Lanka", only a few participants were aware of the fact. This reflects, that public health related messages of importance are not adequately transmitted to the population. Thus, it is mandatory to explore means to transmit relevant messages using social media or mobile apps, which may reach a higher proportion of younger generation, which comprised of majority of the current study population as well.

The knowledge related to tobacco cessation counseling was assessed by following statements. "Five "R" concept can be used in counseling a client who is unwilling to quit SLT use" and "SLT users can be given existing drugs prescribed to combat cigarette craving". Both statements received low number of correct answers, prior to the workshop, which improved in the post workshop analysis. However, an improvement in knowledge does not directly translate into gaining of skills or confidence to practice tobacco cessation counseling. Thus further programmes are necessary with strategies such as role play to enhance tobacco cessation counseling skills, as indicated by the study population itself.

The present study did not analyze the tobacco usage practices of the study population. However, it can be concluded that tobacco usage was very low among female nursing students which comprised of majority of the study sample, due to cultural influences. Thus they are better suited to give SLT/AN cessation advice, because according to literature outcome is better when tobacco cessation advice is provided by non-tobacco users [20].

A Cochrane review by Rice et al., (2017) [21], showed moderate quality evidence to support that advice and support from nurses could increase people's success in quitting smoking, whether in hospitals or in community settings. Though, literature does not reveal any studies related to SLT/AN cessation programmes conducted by nurses, another Cochrane review by Ebbert et al., (2015) summarizes that both pharmacological and behavioral interventions may help SLT users to quit. In contrast, Nethan et al., (2018), in their systematic review indicates that behavioral interventions alone showed high efficacy in SLT cessation among adults with quit rate between 9 - 51.5 per cent, at six months. Thus, these evidences are sufficient to initiate SLT/AN related behavioral interventions by nurses as a first step [22-23].

The time available and focus on acute care in a hospital set up may act as a barrier for effective SLT/AN cessation counseling. However, studies have shown that effective tobacco cessation counseling could even be given at emergency care departments [24-25].

Majority of the nursing students who took part in the study believed that TCC should be a part of the regular treatment modalities and that proper counseling would lead patient to quit the habit. Thus it is timely to consider these sentiments of positivity and incorporate nursing fraternity to the SLT/AN cessation counseling task force, after formulating policy decisions.

The workshop was conducted using a series of lectures. Therefore, though there is an improvement in knowledge, participants may not have been able to gain skills and confidence required to deliver successful SLT/AN counseling via the present workshop, which could be considered as a limitation. Thus continuous training programs aimed at acquiring above mentioned skills will be a future requirement.

In conclusion, workshops are a cost effective method to improve awareness related to SLT/AN cessation counseling. Nursing staff either at hospital or community setting would be an ideal choice to deliver such advice. Further, this model is very useful in the low economical settings.

Acknowledgements

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RESEARCH ARTICLE

Epidemiological and Clinical Data in Low and Intermediate Risk Neuroblastoma: A Single Institution Experience and Survival Outcomes in Jerusalem

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Abstract

Objective: The aim of this study is to evaluate survival outcomes in neuroblastoma patients referred to Augusta Victoria hospital, Jerusalem between 2009 and 2018. **Methods:** This is a retrospective study of clinical and epidemiological data evaluating 34 low and intermediate risk neuroblastoma patients treated at a paediatric hematology/oncology center. Information of demographic, treatment modalities, and survival outcome were abstracted from patients medical records. **Results:** Diagnosing neuroblastoma is challenging due to its wide range of signs and symptoms. In this study, 34 patients were included, with a male to female ratio of 1:26 :1.0. The most common location of the tumor is the abdomen followed by the mediastinal region. Forthy one percent of the cases presented with metastasis, mainly to the liver (20%), bone marrow (15%), and the lymph nodes (6%). Overall survival for Low risk neuroblastoma is 100% while the Intermediate risk neuroblastoma had a 93.1% chance of survival. **Conclusion:** The outcome and prognosis of low risk and intermediate risk Neuroblastoma is excellent as it is seen in developed countries. More attention is needed for early detection and early treatment could improve survival.

Keywords: Neuroblastoma- risk stratification- survival

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Introduction

Neuroblastoma has been the second most common solid tumour in children younger than 15 years of age, occupying 8% of all cancers, with an overall primacy to Leukaemia , brain tumours, lymphomas, respectively. Approximately, 130 new cases of cancer are identified each year per million children in the same age group, with a peak in the first three years of life followed by a decline until the age of 9. On the other hand, a second peak arises in adolescence, taking into consideration that different types of cancers has its own age-distribution pat-tern [1]. However, Survival rates for children have shown improvement during the last decade, the most dramatic improvements occurring among patients with leukemia (48% 5-year relative survival in 1975-1979 versus 84% in 2003-2009), non-Hodgkin's lymphoma (47% versus 85%), and others [2].

As the most common malignancy representing al-most 20% among all neonatal cancers [3], neuroblastoma is derived from neuroepithelial cells developing to form the sympathetic nervous system [4]. It is known for its obscure and preplexed behaviour, some have a regressing turn or maturation process, and some are aggressive despite the different modalities of treatment [5-6].

Materials and Methods

This is a unicentric retrospective study done at Augusta Victoria hospital (AVH) in Jerusalem, from January

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2009 until December 2018, which has been the main referral centre for Palestinian children, considering it is the first and main paediatric hemato-oncology centre in the West Bank and Gaza strip, located in east Jerusalem. It concluded 49 patients from all different districts of the above mentioned areas, who were admitted to our centre to receive treatment, all of which were under the age of 15. The medical record for each patient was used to obtain the information. All of them had given informed consent for the data.

The diagnosis of neuroblastoma was established based upon the biopsy of the tumour itself with a histopathology examination with immunohistochemical stains, bilateral bone marrow study and urine catecholamines after the review of history, physical examination, laboratory information and radiological studies. Body CT scans were run on all patients to define the primary tumour and the extent of metastasis. Other investigation to complete staging were isotope bone scans and MIBG when available. Tissue samples were obtained through tru cut needle biopsy or an open biopsy, preserved in paraffin block at time of diagnosis along with some fresh tissue sent for biological studies for MYCN gene. Two patients had a case revision histopathology scan after their surgery. bilateral iliac bone punctures were carried on for every patient. MYCN Oncogene amplification measurement were carried out through florescent in situ hybridization method (FISH), at another centre due to lack of facilities, as it is believed to be amplified if more than 10 copies were established per cell. All routine tests were carried out on each patient before starting every cycle of the chemotherapy, comprising hepatic, renal and haematological function, in addition to an echocardiogram whenever needed.

Then, the patients were categorized into stage 1, 2, 3, 4, and 4S, applying the criteria from International Neuroblastoma Staging System (INSS) (Table 1).

All patients in the paediatric Hematology/oncology department at Augusta Victoria Hospital were classified into risks and treated by the international protocol of standard treatment of Children's Oncology Group (COG). One case underwent the europian protocol. Low risk neuroblastoma patients either received no treatment (watchful waiting), partial or complete surgical resection, or chemo-therapy, or a combination of the above mentioned. The current COG protocol (ANBL0531: Response-and Biology-based Therapy for Intermediate-risk Neuroblastoma) was used for intermediate risk group.

High risk group were referred to another centre where autologous bone marrow transplant is available.

The full time period of treatment for low risk patients is from observation or surgery alone or maximum 2 cycles of chemotherapy in case tumor only biopsied or tumor resection less than 50%. For intermediate risk patients ranging from 2 cycles to maximum 8 cycles, follow up period is 5 years, each cycle of chemotherapy is due every 21 days. The outcome results were classified as complete remission, stable disease, refractory disease or tumor recurrence. Complete remission is defined as disease-free status. The stable disease means those who had initial response to treatment then the tumour showed no response to further chemotherapy and is surgically unresectable but no change in size is shown with follow up.

Results

Through this period, (January 2009- December 2018), 49 patients were diagnosed with neuroblastoma. Of them, 15 cases were transferred to another medical centres either without any intervention, or after diagnosis and staging as those cases were classified as high risk patients, some of them received induction chemotherapy then transferred to a center where autologous bone marrow transplant facility is available.

IBM SPSS Statistics data editor was used to analyze the data.

As such, 34 eligible patients were included in the study with a clear past history of either chemotherapy or radiotherapy, 19 males and 15 female cases.

Median age at diagnosis is 10.29 months, ranging around the antenatal life which was confirmed soon after birth and 8 years old. Of those, the category of 0-12 months old patients presented the vast majority with of 28 individuals (82%), 4 patients were between 13-24 months old (12%), and 2 patients were 24 months and older (6%).

A male predominance was slight comparing the overall Male: Female ratio of 1.26:1.0.

As for the primary site of the tumour, the most common site is the abdomen (17), then meditational region (11), cervical (2), pelvic (3) and indeterminate bi-adrenal and cervical area (1), with percentages shown in Figure 1.

Of the tumours of an abdominal origin, 11 (26%) originated in the left adrenal gland, 3 (14%) in the right adrenal gland, two (2%) occurred bilaterally in each adrenal gland, and 1 (5%) was in the retroperitoneal area.

In Table 2, the patients are viewed in order of the time of presentation with the most important characteristics.

At presentation, the most prominent symptoms are abdominal distension (8 patients (23.5%)), then fever (6) (17.6%), neck swelling (3) (7%), respiratory distress (2) (5.8%), cough (2) (5.8%), periorbital ecchymosis (2) (5.8%), and others. Three patients were totally

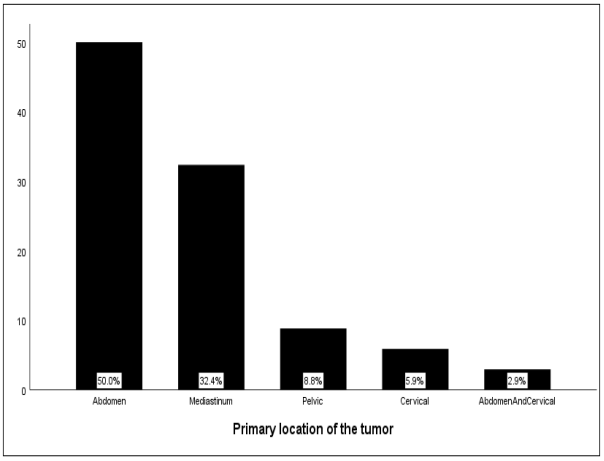

Figure 1. Primary Locations of Neuroblastoma

Table 1. International Neuroblastoma Staging System [7]

Stage	Definition
1	Localized tumour that is completely resected and may or may not have microscopic residual disease; the representative ipsilateral lymph nodes are negative (the nodules attached to and removed along with the tumour may be positive).
2A	Localized tumour that is not completely resected; representative ipsilateral non-adherent lymph nodes are microscopically negative for the tumour
2B	Localized tumour that may or may not be completely resected with non-adherent ipsilateral lymph nodes that are positive for the tumour; lymph nodes must be microscopically negative.
3	Unilateral tumour that extending through the midline, with or without regional lymph node involvement; unilateral tumour with involvement of regional contralateral lymph nodes; or midline tumour with bilateral extension through (unresectable) infiltration or lymph node involvement.
4	Any primary tumour that spreads to distant lymph nodes, bones, bone marrow, the liver, skin, or other organs (except as defined in stage 4S).
4S	Primary localized tumour (as defined for stages 1, 2A or 2B) with limited dissemination to the skin, liver or bone marrow (limited to children under 1 year of age).

asymptomatic when they were found to have a mass unrelated to their original com-plaint, or during a regular checkup, in addition to two patients were discovered to have the tumour while going through maternal antenatal care screening.

Other symptoms included dyspnea, constipation, abdominal pain, stridor, dysphagia, elevated blood pressure, vomiting, anemia, lower limb weakness and shoulder pain. 22 out of 34 cases had more than one symptom simultaneously at presentation (64.7%). 59% of the cases had no metastasis at time of diagnosis, but of those whom metastasis is present, 20% are liver metastasis, while 15% are bone marrow involvement, and 6% had lymph node metastasis. By age, from the 41% of overall metastatic cases at presentation, 32% were between the age of 0- 12 months, then 9% to 13-24 months.

To approach the diagnosis of neuroblastoma, 94% of cases were successful to obtain a biopsy for pathology examination. Then urine catecholamine and biological studies were drawn and sent to an-other hospital due to lack of facility. Of the 94%, 47% were nonfavorable pathology, 18% were favorable, and 29% were indeterminate.

Thus, our diagnosis was based upon the histopathology reports obtained after taking a biopsy of the mass.

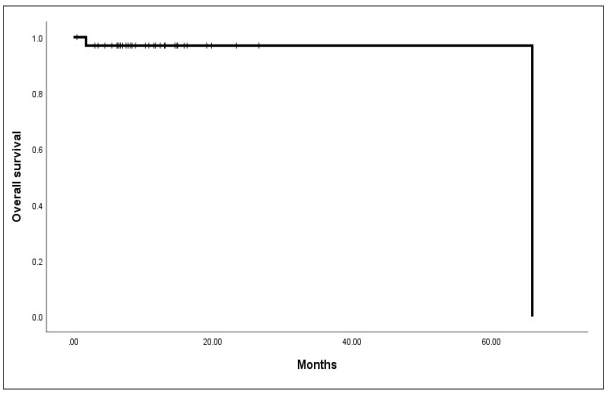

Figure 2. Kaplan Meier Curve for Overall Survival

Otherwise, one case was diagnosed by bone marrow biopsy and one case was started empirically on chemotherapy due to a life-threatening respiratory compromise caused by a mediastinal mass with severe tracheal compression.

Subsequently, MYCN amplification study was done on 24 patients (71%), all were nonamplified, the rest are considered as unknown biological feature. Urine for vanillylmandelic acid is tested in 22 cases (65%) of all individuals , it outstanded as elevated in 14 patients (41%), and not elevated in 8 patients (24%). Lack of fund persisted as an obstacle in completing the MYCN amplification test and urine for VMA for the later patients, as those two tests are done at another hospital.

With reference to the INSS system, 44% were classified as 3, 26% were stage 4, 21% were stage 4s, 9% were stage 1 and 0% are stage 2. According to the risk stratification, 29 patients were an intermediate risk (85%), and 5 low risk (15%) [6].

Looking at the outcome based on the risk stratification, the low risk NB group had a 100% survival rate. Whilst the intermediate risk NB group, it has a 93.1% survival rate.

Two mortality cases were encountered, both were females intermediate risk neuroblastomas; the first one is a neonatal stage 4 with massive hepatomegaly and BM involvement > 10%, it experienced progression on treatment and was transferred to another center and later died despite aggressive chemotherapy and autologous stem cell transplant. Another patient, the second case (age > 1 y , stage III mediastinal FH) underwent remission after surgery and chemotherapy, followed by cervical lymph node recurrence of the tumour after two years. Kaplan Meier's curves for survival was used to demonstrate the cases in Figure 2. General acute complications among the management were acute infections as yeast sepsis or bacterial sepsis. The long term complications observed due to tumor effect were Horner syndrome, scoliosis and poor growth and permanent lower limb paralysis.

Discussion

Neuroblastoma is the most common extra cranial solid tumour in children, it accounts approximately for

Table 2. Neuroblastoma Patients Characteristics with Disease Out come from 2009-2018

Patient's Number	Age	Sex	Location	MYCN Amplification	Stage	Risk	Treatment	Outcome
1	10 mos	F	Mediastinum	non-amplified	3	IR	COG IR	Stable disease
2	6 mos	M	Sacrum	non-amplified	3	IR	COG IR	Complete remission
3	4 yrs	F	Mediastinum	non-amplified	3	IR	Europian protocol for IR NB	Recurrence, Died.
4	4 mos	F	Left Adrenal	Unknown	4s	IR	COG IR	Complete remission
5	7 mos	F	Mediastinum	Unknown	3	IR	COG IR	Complete remission
6	10 mos	F	Cervical	non-amplified	3	IR	COG IR	Complete remission
7	7 yrs	M	Left Adrenal	non-amplified	1	LR	Watchful waiting	Complete remission
8	7 mos	M	Mediastinum	non-amplified	3	IR	COG IR	Complete remission
9	8 mos	M	Left adrenal	non-amplified	4	IR	COG IR	Complete remission
10	Antenatally	M	Left adrenal	Unknown	1	LR	Watchful waiting	Complete remission
11	1 yr	M	Right adrenal	non-amplified	3	IR	COG IR	Complete remission
12	1 mos	F	Liver	Unknown	4s	IR	COG IR	Complete remission
13	1 mos	F	Left adrenal	Unknown	3	LR	Watchful waiting	Complete remission
14	1 mos	F	Right adrenal	Non-amplified	4	IR	COG IR	Refractory, Died.
15	3 mos	M	Cervical	Unknown	4	IR	COG IR	Complete remission
16	2 mos	M	Adrenal; Bilateral	non-amplified	4	LR	Watchful waiting	Complete remission
17	3 mos	F	Left adrenal	non-amp	4s	IR	COG IR	Complete remission
18	1.2 yrs	M	Left adrenal	non-amplified	4	IR	COG IR	Complete remission
19	Antenatally	M	Right adrenal	non-amplified	4s	IR	COG IR	Complete remission
20	7 mos	F	Mediastinum	non-amplified	3	IR	COG IR	Complete remission
21	1 yr	F	Left adrenal	Unknown	1	LR	Excisional Biobsy	Complete remission
22	6 mos	F	Mediastinum	Unknown	3	IR	COG IR	Stable disease
23	2 mos	F	Abdomen	non-amplified	4s	IR	COG IR	Stable disease
24	2 mos	M	Adrenal; Bilateral	non-amplified	4s	IR	COG IR	Complete remission
25	5 mos	F	Left adrenal	non-amplified	4s	IR	COG IR	Stable disease
26	1 yr	M	Pelvic	Unknown	3	IR	COG IR	Complete remission
27	6 mos	F	Left adrenal	non-amplified	4	IR	COG IR	Complete remission
28	1 yr	M	Mediastinum	non-amplified	4	IR	COG IR	Stable disease
29	7 mos	M	Mediastinum	non-amplified	4	IR	COG IR	Stable disease
30	2 mos	M	Mediastinum	Unknown	3	IR	COG IR	Complete remission
31	1.5 yrs	M	Mediastinum	non-amplified	3	IR	COG IR	Stable disease
32	6 mos	M	Pelvic	non-amplified	3	IR	COG IR	Complete remission
33	1.2 yrs	M	Abdomen; retroperitoneal space	non-amplified	4	IR	COG IR	Stable disease
34	9 mos	M	Mediastinum	non-amplified	3	IR	COG IR	Complete remission

i.e, Mos, months; Yrs, years; F, female; M, male; IR, intermediate risk; LR, low risk; COG IR, Children oncology group protocol for Intermediate risk neuroblastoma.

8% of all childhood cancers. Detecting and diagnosing neuroblastoma is challenging mostly due to its variable and nonspecific signs and symptoms. Risk stratification is very important in determining the treatment strategy and prognosis, it depends on the patient's age and stage at diagnosis, MYCN status as a biological factor, histopathological classification plus the DNA pleiody [1-8].

MYCN amplification has shown relation to determining the aggressiveness of neuroblastoma as it is in 16-25% of cases [9-10], in addition to Anaplastic lymphoma kinase gene (ALK) which is a major predisposition to familial neuroblastoma [11]. Happening that MYCN amplification and ALK gene mutation might get-together in the same case produces a poor output suggesting a cooperation between the two [12].

Patients are classified into low, intermediate, and high risk groups based on the age, stage, MYCN status and histology, while the prognosis is based on risk type, response to treatment, and the time interval between diagnosis and recurrence (relapse cases) [13].

Patients of all ages with stage 1, 2, or 4S disease without MYCN amplification have an excellent prognosis with a 5-year survival rate of over 95%. Patients with stage 3, as well as infants with stage 4 neuroblastoma without MYCN amplification have a survival rate of approximately 75%. Children (>1 year) with stage 4 neuroblastoma (regardless of MYCN status), MYCN amplified stage 2 and 3 disease, as well as infants less than 1 year with metastatic, MYCN amplified disease has

around 30% chance of recovery [14].

Here in our study, the most prevalent symptom was abdominal distention, taking into consideration that many patients presented with more than one com-plaint. Other than this, the symptoms occurred related to the location of the tumour, thus, some cases had an abdominal distention alongside with constipation or vomiting. On the other hand, patients presented with cervical or mediastineal mass had respiratory symptoms, explaining cough, stridor, or, with more complexity, a respiratory tract infection. Other symptoms were fever, periorbital ecchymosis, and anemia suggested metastasis.

A small percentage were asymptomatic and were dis-covered by doing a physical exam or a radiological study for yet another reason not related to the diagnosis of neuroblastoma. Ages by which the disease was diagnosed at had a median of 21.09 months for all risk types, a study by London, W. B. et al showed the that median age at diagnosis is 18 months [15], this can be explained by our small sample size. The primary site of the tumor were, in order, the abdomen, mediastinum, cervical , pelvic regions.

As for metastasis of LR and IR group, the most common site is the liver, then the bone marrow and lymph nodes. In our study, 85% of our cases were of an intermediate risk and 15% were low risk. High risk patients were transferred to another centers due to lack of facilities. Most of them were under the age of one year. Looking at the outcome results, low risk neuroblastoma patients had a 100% 5-year survival, while the intermediate risk had a percentage of 93%. as more than one study approved that increasing age is associated with worse outcome results [16-17], Pinto et al clarified in his research the low risk neuroblastoma patients more than 95% chance of survival at 5-year follow up, and intermediate risk neuroblastoma between 90 and 95% at the same time interval [18], our better survival results in IR group is mostly is because that majority of the patients are less than 1 year (82%).

Survival post-relapse is dismal, A study by Garaventa et al [19], showed that the Survival of children with recurrent neuroblastoma is very poor. Treatment complications were bacterial and fungal infections and sepsis. Long term sequelae which are related to the tumor effect are the most dramatic as in our patients that included Horner syndrome, scoliosis, and permanent lower limb paralysis.

Looking into limitations, AVH has been a referral centre since 2008 from the West Bank and Gaza Strip for Palestinian children, so the load on the hospital had become overstrained at some points. In 2012, two centres opened in the west bank, so cases are shared between AVH and them. Lack of enough instrumentation has always been a chal-lenge till this day.

Funding and coverage of some important studies including biological study, and imaging, mainly MIBG, is a major challenge for optimal staging and management of neuroblastoma cases in Palestine. Finally, number of cases of neuroblastoma are ex-pected to increase as the populations grows in the previously mentioned districts, but the diagnosis of Neuroblastoma itself is still a stump due to the tumour's perplexed presentation and behaviour and not enough tools to diagnose it.

In conclusion, the outcome and prognosis of low risk and inter-mediate risk Neuroblastoma is excellent as in developed countries, more attention and medical awareness for early detection and treatment of IR neuroblastoma to minimize severe long term tu-mour morbidities in these groups is crucial.

Funding

This study did not receive any funding.

Conflict of interests

The authors have no conflicts to declare.

Abbreviations

NB, Neuroblastoma; LR, Low risk; IR, Intermediate risk; HR, High risk; FISH, florescent in situ hybridization method; VMA, Vanillylmandelic acid.

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RESEARCH ARTICLE

Cancer Incidence in Nepal: A Three-Year Trend Analysis 2013-2015

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Abstract

Background: Cancer is an major public health problem in the world. This study aims to present a three-year trend of cancer incidence in Nepal. **Methods:** This study used the three-year data of National Cancer Registry Program (NCRP) from January 2013 to December 2015. NCRP currently includes 12 major hospitals where diagnostic treatment facilities are available and represent the majority of the cases in Nepal. Descriptive analysis was used to present the demographic profile of the participants and the incidence of different topography of cancer. Age-specific and age-adjusted cancer incidence per 100,000 population were presented. **Results:** A total of 27,483 new cancer cases were included in the study. The age-adjusted incidence rates were 39.1, 39.8 and 41.8 per 100,000 population in the year 2013, 2014 and 2015 respectively. The most common cancer in Nepal was lung followed by cervical, breast, stomach and colorectal cancer. Among males, lung cancer was the most common followed by lip and oral cavity, stomach, colorectal cancer and leukemia and among females, cervical cancer followed by breast, lung, ovary and stomach. **Conclusion:** Cancer incidence is rising in Nepal and thus comprehensive policies targeting prevention, early detection, and treatment programs should be carried out.

Keywords: Epidemiology- Neoplasms- registries- prevention and control- Nepal

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Introduction

Cancer is a major public health problem and it has become one of the leading cause of deaths worldwide. Globally, nearly 18.1 million new cancer cases and 9.6 million cancer deaths occurred in 2018 with 70% deaths occurring in developing countries of the world [1]. By 2040, it is estimated that the new cases of cancer will rise to 29.5 million [1]. Increase in life expectancy, changes in lifestyle related factors like food habits, sedentary lifestyle, sexual behaviour, environmental pollution due to industrialization are mainly related to increasing the burden of cancer incidence and deaths in developing countries [2]. Likewise, low level of awareness of people on cancer and low screening rate has additionally raised the burden of cancer which is especially diagnosed at a late stage. This challenges the existing healthcare system with added economic burden in health economy of especially those of low- and middle-income countries [3]. GLOBOCAN 2018 estimates that the age-standardized cancer incidence and mortality rates in Nepal to be 103.7 and 77.8 per 100,000 population in Nepal [4]. Previous studies have shown that the cancer burden in Nepal may still rise in future and poses a serious threat [5].

The National Cancer Registry Program (NCRP) of Nepal routinely collects data on cancer patients' information

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including demographics, primary tumour sites and tumour morphology from 12 major hospitals of Nepal. B.P. Koirala Memorial Cancer Hospital (BPKMCH) is responsible for collecting, evaluating and publishing national cancer statistics [6-7]. This study aimed to present the trend of 3-year registry data of new cancers registered in the NCRP between January 2013 and December 2015.

Materials and Methods

The Department of Cancer Prevention, Control and Research, BPKMCH is responsible to collect and analyze the data from 12 cancer centres for National cancer registry Program. The hospitals included are BPKMCH (Chitwan), Bhaktapur Cancer Hospital (Bhaktapur), Bir Hospital (Kathmandu), TU Teaching Hospital (Kathmandu), Kanti Children's Hospital (Kathmandu), B. P. Koirala Institute of Health Sciences (Sunsari), Manipal Teaching Hospital (Pokhara), Paropakar Maternity and Women's Hospital (Kathmandu), Patan Academy of Health Sciences (Lalitpur), Civil Service Hospital (Kathmandu), Shree Birendra Army Hospital (Kathmandu) and Nepalgunj Medical College Teaching Hospital (Nepalgunj [7]. These 12 hospitals have the diagnostic as well as treatment facilities and represent the majority of the cases in Nepal. This study used data collected by NCRP to present the trend of cancer incidence in Nepal in a three-year period from January 2013 to December 2015 [8-10]. The data were collected using a standardized semi-structured form consisting of socio-demographic characteristics, detail of diagnosis, clinical stage and treatment. In order to avoid double and multiple entries of the cases, the database was verified by name, age, sex, address, topography and morphology of cancer cases. The data were entered, cleaned, removed duplicates and analysed using in excel 2016. Descriptive analysis was used to present the demographic profile of the participants and the incidence of different topography of cancer according to the gender and their related variables. Age-specific and age-adjusted cancer incidence were also presented. For age-specific crude incidence rate, we used population data for 2013-2015 medium variant predicted by the Central Bureau of Statistics [11] and to adjust the age we used Segi World Standard Population. Cancer cases were categorized as per the international classification of disease for oncology (ICD-10). Permission was taken prior to the study from B.P. Koirala Memorial Cancer Hospital, Nepal.

Results

The total number of new cases from 12 hospitals were 8882 in 2013, 9221 in 2014 and 9851 in 2015. Out of which, 471 cases were non-Nepalese and were excluded from the analysis. The total number of new cases included in this study were 8729 in 2013, 9036 in 2014 and 9718 in 2015. Male consists of 45% and female were 55% of the cases (Table 1). Majority of the cases were married. About 33% of the cases were from Province 3 followed by Province 1 (19%) and Province 5 (15%).

Top Cancer in Nepal

The most common cancer in Nepal was lung followed by cervical cancer, breast, stomach and colorectal cancer (Table 2). The top leading cancer site among males was lung followed by lip and oral cavity, stomach, colorectal cancer and leukaemia. Likewise, among females, it was cervical uteri followed by breast, lung, ovary and stomach (Table 3).

Cancer Incidence

The incidence of cancer was seen increasing with the increase in age and the incidence was seen more in the age group 70-74 years in 2013. Similarly, the incidence was also seen increasing with age in 2014 and 2015 but it was found more in the age group 60-64 years. A similar pattern was seen in the incidence among the male population. However, the incidence increase with age in females with age group 45-49, 50-54 and 60-64 being the most common age group in the year 2013, 2014 and 2015 respectively. After this age group, the incidence in females was seen decreasing with age (Table 4).

The age-specific incidence rate (ASIR) was observed more in the age group 80 and above in overall (218 per 100,000 in 2015) and male population (303 per 100,000 in 2015) and 60-64 years in case of the female population (170 per 100,000 in 2015) in all the three-year period. The ASIR increased with increase in age. However, we also found that the ASIR decreased in the age group 75-79 years then increased in 80 and above population in both males and females. The ASIR in females also decreased in the age group 65-69 years. The total ASIR in females is more than that of males in 2013-2015. The ASIRs in age groups less than 30 years and more than 60 years were more than in males than females. The female ASIR increased in consecutive years but slightly decreased in males in the year 2014 (Table 5). Similarly, with age adjustment, the incidence rate in the total population was found to be increasing in consecutive years (39.1, 39.8 and 41.8 per 100,000 in the year 2013, 2014 and 2015 respectively). However, the age-adjusted incidence rate (AAIR) among male slightly decreased in 2014 (37.0, 36.5 and 39.9 per 100,000 in 2013, 2014 and 2015). In contrast, AAIR among female increased in 2014 then slightly decreased in 2015 (41.0, 43.9 and 43.4 per 100,000 in 2013, 2014 and 2015) (Figure 1).

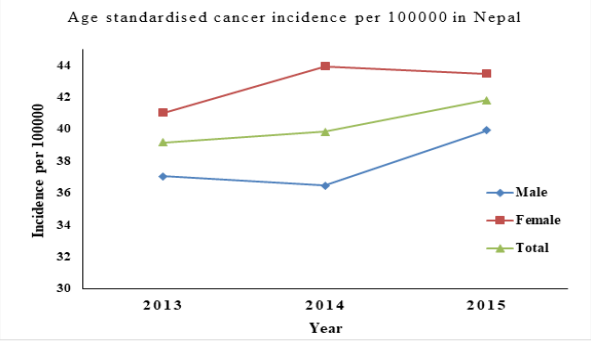

Figure 1. Age Adjusted Cancer Incidence Rate per 100,000 Populations in Nepal.

Table 1. Characteristics of New Cancer Cases in Nepal 2013-2014

Characteristics	Year n (%)		
	2013	2014	2015
Gender			
Male	4,011 (46.0)	4,014 (44.4)	4,483 (46.1)
Female	4,718 (54.0)	5,022 (55.6)	5,235 (53.9)
Marital status			
Unmarried	245 (2.8)	184 (2.0)	145 (1.5)
Married	5,613 (64.3)	5,892 (65.2)	6064 (62.4)
Widow/ Divorced/ Separated	174 (2.0)	183 (2.0)	221 (2.3)
Not available	2,377 (27.2)	2,454 (27.2)	2763 (28.4)
Not applicable (<15 years)	320 (3.7)	323 (3.6)	525 (5.4)
Province			
Province 1	1694 (19.4)	1794 (19.9)	1825 (18.8)
Province 2	1139 (13.0)	1203 (13.3)	1210 (12.5)
Province 3	2790 (32.0)	2919 (32.3)	3265 (33.6)
Province 4	1066 (12.2)	997 (11.0)	1173 (12.1)
Province 5	1304 (14.9)	1362 (15.1)	1481 (15.2)
Province 6	193 (2.2)	249 (2.8)	253 (2.6)
Province 7	310 (3.6)	308 (3.4)	340 (3.5)
Unknown	233 (2.7)	204 (2.3)	171 (1.8)
Total	8729 (100.0)	9036 (100.0)	9718 (100.0)

Table 2. Top 10 Cancers in Nepal 2013-2015

S.N	Topography	N (%)
1	C33-34 Lung	3737 (13.60)
2	C53 Cervix uteri	2552 (9.29)
3	C50 Breast	2456 (8.94)
4	C16 Stomach	1574 (5.73)
5	C18-21 Colorectal	1457 (5.30)
6	C00-06 Lip, oral cavity	1426 (5.19)
7	C91-95 Leukemia	1259 (4.58)
8	C32 Larynx	1085 (3.95)
9	C56 Ovary	1065 (3.88)
10	C23 Gall bladder	911 (3.31)

Discussion

The present analysis was based on a total of 27,483 new cancer cases diagnosed in Nepal from 12 hospitals from 2013 to 2015. Cases reported in 2015 (n=9718) was 11% higher than that in 2013 (n=8729). NCRP Nepal data shows an increased incidence of cancer in Nepal from 2013 (ASIR=39.1 per 100,000) to 2015 (ASIR=41.8 per 100,000). It has been estimated by WHO that the incidence for the year 2018 to be 18.1 million cases globally which in 2040 will increase to 29.9 million [1]. Increase in life expectancy, changes in lifestyle related factors like diet, physical activity, sexual habit, environmental pollution due to industrialization might boost up in increasing the cancer incidence in Nepal. The incidence of cancer was observed to be increasing with age. Advancing age is one of the important risk factors for the overall cancer. The duration of exposure to multiple risk factors like chronic infection, unhealthy lifestyle involving tobacco and alcohol use, stress, lack of regular physical activity and poor dietary pattern, obesity, increases with advancing age [12].

The study highlights that female occupies more cancer burden than the male. The reason might be among the top 10 cancers in Nepal, the female site-specific cancer i.e cervical, breast and ovary occupy the major portion. In addition, this study showed females were affected at an earlier age than the males with age group 45-64 years being the commonest. Lung cancer was the most common cancer in men in Nepal, followed by lip/oral cavity, stomach and colorectal cancers. Cervical and breast cancers were the most common cancer in female followed by lung, ovary and stomach cancers. This trend of cancer was found to be similar to the trend in 2002 to 2012 NCRP report [6]. Thus, lung cancer, cervical cancer, breast cancer, stomach cancer, colorectal cancer and oral cancers are major cancer burden of the country. Province 3 occupies higher burden of cancer and Province 6 and 7 the least [13]. The reason might be the availability of health facilities and diagnostic centres and also the socio-economic status. Kathmandu, the capital city of Nepal is located in Province 3 and comprised of many tertiary health institutions as well as the diagnostic centres [14]. In contrast, Province 6 and 7 have less number of diagnostic facilities for cancer and the people are socio-economically weak. Thus, many will not be diagnosed and missed in the cancer registry.

Lung cancer is the leading cause of cancer in Nepal and throughout the world. The incidence of oral cancer

Table 3. Top 10 Cancers among the Male and Female Population in Nepal 2013-2015

S.N	Top Male Cancers	n (%)	Top Female Cancers	n (%)
1	C33-34 Lung	2121 (16.96)	C53 Cervix uteri	2552 (17.04)
2	C00-06 Lip, oral cavity	1047 (8.37)	C50 Breast	2392 (15.97)
3	C16 Stomach	909 (7.27)	C33-34 Lung	1616 (10.79)
4	C18-21 Colorectal	812 (6.49)	C56 Ovary	1065 (7.11)
5	C91-95 Leukemia	773 (6.18)	C16 Stomach	665 (4.44)
6	C32 Larynx	751 (6.00)	C18-21 Colorectal	645 (4.31)
7	C67 Bladder	547 (4.37)	C23 Gall bladder	616 (4.11)
8	C70-72 Brain and CNS	419 (3.35)	C91-95 Leukemia	486 (3.25)
9	C22 Liver	374 (2.99)	C73 Thyroid	414 (2.76)
10	C85 Non-Hodgkin Lymphoma	353 (2.82)	C00-06 Lip, oral cavity	379 (2.53)

Table 4. Distribution of Cancer Cases by Age Group and Gender

Age group	Male			Female			Total		
(years)	2013	2014	2015	2013	2014	2015	2013	2014	2015
0-4	60	48	114	27	36	55	87	84	169
5-9	64	61	116	32	42	66	96	103	182
10-14	71	89	110	66	47	64	137	136	174
15-19	69	88	89	77	67	87	146	155	176
20-24	100	85	111	97	111	117	197	196	228
25-29	90	88	124	139	166	139	229	254	263
30-34	144	140	149	195	234	212	339	374	361
35-39	162	146	188	325	309	331	487	455	519
40-44	209	228	241	444	486	505	653	714	746
45-49	225	249	263	575	584	588	800	833	851
50-54	328	379	433	563	627	641	891	1006	1074
55-59	438	450	419	503	603	605	941	1053	1024
60-64	495	554	595	556	596	649	1051	1150	1244
65-69	448	458	500	407	457	503	855	915	1003
70-74	649	504	498	448	355	369	1097	859	867
75-79	248	269	295	148	166	190	396	435	485
80+	211	178	238	116	136	114	327	314	352
Total	4,011	4,014	4,483	4,718	5,022	5,235	8729	9036	9718

is increasing in both men and women ranking the second highest cancer among men and 10th in women. Both these cancers are attributed to increased exposure to any form of tobacco i.e chewing and smoking [15]. According to STEPS Survey Nepal, tobacco smoking proportion in Nepalese population is 18.5% (men 27.0% and women 10.3%) and for smokeless tobacco use it is 17.8% (men 31.3% and women 4.8%) [16]. The government of Nepal has undertaken a number of tobacco control initiatives which includes most of the important provisions of the Framework Convention, i.e. prohibition of smoking in public places, on public transport and in workplaces; ban on all forms of tobacco advertisement, promotion and sponsorship; pictorial health warnings in cigarette, bidi and other tobacco packets; prohibition of sale of tobacco to and by minors and pregnant women; establishment of a tobacco control and regulatory committee; establishment of a health tax fund, etc. [17-18]. Although tobacco control legislation and policies exist in Nepal, they have to be implemented effectively.

Over the year, cervix and breast cancers have increased in Nepal. Creating awareness on cervical cancer, vaccination against HPV and regular screening for cervical cancer help in early detection and prevention of cervical cancer [19]. Similarly, regular self-examination, periodic clinical breast examination and mammogram are excellent ways of detection of early stage of breast cancer [20]. Despite being early detectable and curable cancers in Nepal, most of the women are diagnosed at late stage [21]. Thus, raising awareness among women on these cancers along with nationwide screening campaigns would aid in early detection and treatment thereby reducing the morbidity and mortality caused by

Table 5. Crude Age Specific Incidence Rate per 100,000 Population in 2013-2015

Age group	Male			Female			Total		
(years)	2013	2014	2015	2013	2014	2015	2013	2014	2015
0-4	4.204	3.295	7.651	1.998	2.664	3.935	3.131	2.968	5.852
5-9	4.367	4.279	8.326	2.283	2.996	4.961	3.348	3.694	6.682
10-14	4.253	5.432	6.866	4.112	2.928	4.166	4.184	4.236	5.545
15-19	4.261	5.324	5.319	4.772	4.152	5.307	4.516	4.719	5.313
20-24	8.172	6.466	7.919	6.869	7.86	7.769	7.474	7.062	7.841
25-29	9.741	9.294	12.626	11.484	13.714	10.94	10.73	11.622	11.675
30-34	17.563	16.825	17.625	18.685	22.422	19.143	18.191	19.605	18.486
35-39	22.034	19.525	24.73	36.428	34.635	35.15	29.925	27.343	30.496
40-44	31.206	33.727	35.289	58.325	63.842	62.545	45.632	48.898	50.055
45-49	37.334	40.594	42.197	89.255	90.652	86.228	64.16	65.27	65.201
50-54	63.413	71.623	80.017	107.007	119.171	112.997	85.396	93.515	96.896
55-59	100.091	101.095	92.41	116.565	139.739	133.264	108.27	118.724	112.85
60-64	136.148	149.865	158.199	149.81	160.588	170.359	143.049	154.293	164.318
65-69	152.479	154.604	166.957	131.477	147.629	157.241	141.704	149.766	161.939
70-74	271.093	213.568	214.017	177.221	140.432	147	222.881	176.038	179.239
75-79	181.788	180.207	186.985	105.314	118.123	111.69	142.984	141.709	147.92
80+	295.854	242.606	303.703	156.918	183.973	137.387	225.14	209.377	218.169
Total	30.35	29.948	32.98	33.6	35.765	36.241	32.024	32.685	34.66

these female-related cancers [22-23].

Stomach, colorectal, oesophagus, gall bladder and liver are also rising cancers in Nepal. The dietary factors like consumption of alcohol, food at very high temperature, fatty junk food, spicy food , low fiber diet, processed meat and red meat and salt preserved foods are the key risk factors for these cancers in Nepal [12].

The overall incidence of cancer in Nepal is in steady rise among both males and females, becoming a major public health problem. This challenges the overall health system of the country in present as well as in near future. Strengthening health system of the country from periphery to tertiary level in cancer prevention, early detection, diagnosis, treatment and palliation is way forward to cope with this rising incidence of cancer. Incorporating cancer control activities in package of essential non-communicable disease (PEN) program would be a significant step towards its prevention. Also, nationwide intervention on control of tobacco consumption would be a cost-effective cancer prevention activity. Furthermore, the top cancers in Nepal i.e. cervical cancer, breast cancer and oral cancer are early detectable and curable, nationwide extensive screening programs, awareness activities, launching HPV vaccination in National immunization program to reduce the load of these cancers.

The major limitation of our study is that NCRP data collection does not cover patients who are diagnosed and treated elsewhere than the 12 included hospitals. However, these hospitals are the major cancer treatment centres with good coverage of the country. Our findings may serve as a baseline for future comparisons and assessment of the overall effectiveness of cancer health care in Nepal and may provide a clue to capture the greatest need.

In conclusion, the incidence of cancer is in increasing trend in Nepal with lung, cervix, breast, stomach and colorectal cancers being the leading cancer sites. This study reflects that cancer is a key public health issue of the current era and the government should focus on all the aspects of cancer control i.e., preventive, curative and rehabilitative services.

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None

Statement Conflict of Interest

None

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RESEARCH ARTICLE

Dosimetric Evaluation of 3-Dimensional Conformal Radiotherapy Technique in Postoperative Patients with Gastric Carcinoma: When Is IMRT Really Needed?

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Abstract

Background and purpose: Adjuvant Chemoradiotherapy is the standard of care for postoperative gastric cancers with high risk features. The purpose of the current study is to do a dosimetric analysis in the postoperative setting by using 3-Dimensional Conformal Radiotherapy (3D-CRT) to a total dose of 45 Gy in 25 fractions over 5 weeks. A subsequent comparison with the 3D-CRT and IMRT of other published data is presented. **Materials and Methods:** Sixty postoperative patients who underwent radiation with 3D-CRT technique were included in this analysis. All patients received concurrent 5-Flurouracil or Capecitabine chemotherapy along with radiation. Radiation plans were analysed in terms of PTV coverage, conformity index (CI), homogeneity index (HI), organs at risk (OARs) and dose volume histogram (DVH) parameters. **Results:** DVH statistics for PTV: Dmean was 45.2±0.8 Gy, D98 was 42.9 ±1 Gy, D95 was 43.4±0.8 Gy, and D2 was 47.7±1.1 Gy. Mean CI for all plans was 1.23±0.43 and HI was 1.09±0.03. DVH parameters for OARs: right kidney, Dmean = 11.9±5.1 Gy, V18 was 21.5±13.8%, V15 was 27.2±14.9% and left kidney, Dmean was 17.7±5.8 Gy, V18 was 33.5±13.8%, V15 was 43.2±15.5%. Dmean for liver was 27.7±6.4 Gy and V20 was 69.2±15.8%. D195cc for the bowel bag was 36.3±10.8 Gy. **Conclusion:** The results of this study and subsequent comparison with existing literature suggests that 3D-CRT provides adequate homogenous target volume dose coverage and OAR protection, comparable to IMRT. More than the radiotherapy technique, it was the anastomotic site and the tumor location that determined the OAR doses.

Keywords: Gastric cancer- Adjuvant 3D-CRT- DVH- conformity index

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Introduction

Stomach cancer is the fifth most common cancer in the world (5.7% of all new cases) and the third most common cause of cancer related death (8.2% of all cancer deaths) [1]. India has a low incidence of stomach cancer compared to world statistics and is the fifth most common cancer in India. The estimated incidence of gastric cancer in India for the year 2018 was 5% (57,394 cases) and about 38,818 new gastric cancer cases were estimated to have occurred in males [2]. Partial or total gastrectomy is the mainstay of treatment in the management of stomach cancer [3]. In the majority of cases, treatment with surgery alone is not satisfactory and the 5-years survival depends on tumour stage and lymph nodal status. Loco-regional recurrence is the major problem in 80-85% of patients [4-5]. Since the introduction of SWOG/INT0116 trial in 2001, adjuvant concurrent chemoradiotherapy (CRT) became the standard of care for gastric cancer [6]. The benefits of adjuvant CRT was extended even for patients with D2 dissection [7]. However, post-operative radiotherapy significantly increases toxicities compared to surgery alone [6]. This has been minimised with the advent of newer technologies like 3D-CRT and IMRT. Superiority of IMRT over 3D-CRT has not been clearly established unlike few other sites [8-9]. The purpose of

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the present study was to do a dosimetric analysis of the doses received in post-operative setting by using 3D-CRT to a total dose of 45 Gy in 25 fractions over five weeks with concurrent chemotherapy. A subsequent comparison with the existing 3D-CRT and IMRT literature was done.

Materials and Methods

This retrospective analysis on dosimetric data in post-operative carcinoma stomach was carried out at the Department of Radiotherapy and Oncology in a multispecialty tertiary care centre in India after informed consent. Being a retrospective dosimetric analysis of patients treated as per institutional protocol, additional ethical clearance was not sought. Case records of all patients with carcinoma stomach (adenocarcinoma and signet ring cell carcinoma) registered in the department between January 2012 and December 2015 were analysed. Out of 156 cases of primary gastric cancer, only 93 (60%) of the cases were histopathologically confirmed to have adenocarcinoma and signet ring cell carcinoma. Out of these, the 60 patients who underwent radical surgery followed by post - operative radiotherapy have been included in this analysis and the rest who received palliative treatment were omitted. All patients received concurrent chemotherapy using 5-FU or capecitabine based regimen. Staging was done according to AJCC 7th edition staging system [10].

Radiotherapy Planning

The post-operative patients of carcinoma of stomach were selected for this dosimetric analysis of the doses received by PTV and OARs using 3D-CRT. All patients underwent total or subtotal gastrectomy with D1 or D2 lymph-nodal dissection. Planning CT scans were taken with patients in supine position using multislice CT scanner with a slice thickness of 2.5mm (GE healthcare technologies, Wankesha, WI, USA). The images were then transferred to EclipseTM treatment planning system (v.8.6, Varian associates, Palo, Alto, CA, USA). Contouring was done as per Tepper and Gunderson guidelines [10-11]. The clinical target volume (CTV) included both post-operative tumour bed and regional lymphatic drainage. The nodal CTV included nodes in the para-aortic (PA), celiac axis, porta hepatis and superior mesenteric artery (SMA) group. All lymph nodal groups were contoured according to the guidelines be Tepper et al [10]. The PA lymph-nodal volume was delineated by giving differential margin to the aorta from thoracic (T11) to lumbar (L2) vertebrae, (i.e. 2.5 cm right side, 2 cm anterior, 1.2 cm left side, and 0.2 cm posterior), 1cm symmetric margin was given to portal vein (from origin of portal vein to porta-hepatis), celiac artery (from origin of celiac axis to its first bifurcation) and superior mesenteric artery (from its origin to 1 cm) (Figure 1). The CTV tumour included the tumour bed, remaining stomach and anastomotic site. Both CTV nodal and CTV tumour were dependent on the primary location of the tumour, pathological T-stage and nodal stage. The CTV total was made by joining both CTV nodal and tumour with the help of Boolean apparatus. PTV was contoured by giving 1 cm symmetric margin around CTV total. OARs including liver, both kidneys, spinal cord, heart, and small bowel were contoured. 3D-CRT plans were generated by using one anterior and two lateral fields with appropriate wedges (Figure 2) with 6 MV photons and treatment was executed by a linear accelerator. A total dose of 45 Gy in 25 fractions were prescribed to the PTV. Plans were optimised whenever required to deliver the prescribed dose to more than 95% of PTV. Dose volume histograms (DVH) were generated and evaluated for all the OARs before delivering the treatment. Evaluation of dosimetric data of the target volumes and OARs was done using Quantitative Analysis of Normal Tissue Effects in Clinics (QUANTEC) parameters [12].

All 3D-CRT plans were analysed in terms of PTV coverage, conformity index (CI), homogeneity index (HI), and OAR dose volume parameters. Several definitions of CI and HI are available but we used the RTOG definitions to calculate the CI and HI.

Conformity index (RTOG definition) = Reference isodose volume / target volume

Homogeneity index = maximum isodose in the target / reference isodose

In an ideal scenario the CI should be equal to 1 and HI should be < 2. CI less than 1 indicates that the target volume is not adequately irradiated and a value greater than 1 signifies that the irradiated volume is greater than the target volume.

Statistics

Statistical analysis was done with the Statistical Program for Social Sciences (SPSS v23, IBM Corp, USA). Descriptive analysis was done for the dosimetric and demographic data. Summary of statistics including mean, range, and standard deviation were obtained.

Results

Patient and treatment characteristics

The median age of patients in our study was 52 years (22-75 years). Most of them were males (33 patients, 55%). Most of the patients were smokers (60%) and occasional

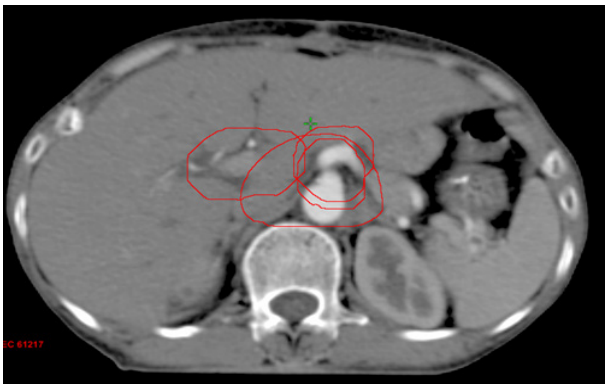

Figure 1. CTV NODAL Contouring; 1cm Symmetric Margin Around Portal Vein, Celiac Artery, Superior Mesenteric Artery; Differential Margin Around Aorta, 2.5 cm right, 2 cm Anterior, 1.2 cm Left, and 0.2 cm Posterior

Table 1. Patient and Disease Characteristics

Characteristic	Number	Percentage (%)
Gender		
Male	33	55%
Female	27	45%
Median age (years)	52 (22-75)	
Smoker	36	60%
Alcoholics	33	55%
Surgery		
Sub-total gastrectomy	54	90%
Total gastrectomy	6	10%
Lymph-node dissection		
D1[a]	40	66%
D2[b]	20	33%

[a]D1 lymph node dissection, stations 1 to 6; along the greater and lesser curvature of stomach; [b]D2 lymph node dissection, D1 and stations 7 to 11; along left gastric artery, common hepatic artery, celiac trunk, and splenic artery.

alcoholics (55%). Five percent of the patients had a family history of malignancy. The common presenting symptoms were loss of appetite, upper abdominal pain and loss of weight. Most of the patients underwent sub-total gastrectomy (90%) with D1 lymph-node dissection (66%) or D2 lymph-node dissection (33%). Adenocarcinoma (intestinal type) was the most common post-operative histopathological variant. All patients underwent post-operative radiotherapy to a total dose of 45 Gy in 25 fractions over 5 weeks using 3D-CRT (Table 1).

Dosimetric parameters of PTV

The mean PTV volume was 848.6±337cc, Dmean was 45.2±0.8 Gy, D98 was 42.9 ±1 Gy, D95 was 43.4±0.8Gy, D50 was 45.2±0.7Gy, D5 was 47.3±1.0Gy and D2 was 47.7±1.1Gy. Mean CI for all plans was 1.23±0.43 and HI was 1.09±0.03 (Table 2).

Dosimetric parameters of OARs

DVH parameters for OARs; right kidney Dmean was 11.9±5.1 Gy, V18 was 21.5±13.8%, V15 was 27.2±14.9%, V13 was 31.7±15.7% and left kidney Dmean was 17.7±5.8 Gy, V18 was 33.5±13.8%, V15 was 43.2±15.5%, V13 was 59±15.6% (Figure 3). Dmean for liver was 27.7±6.4Gy

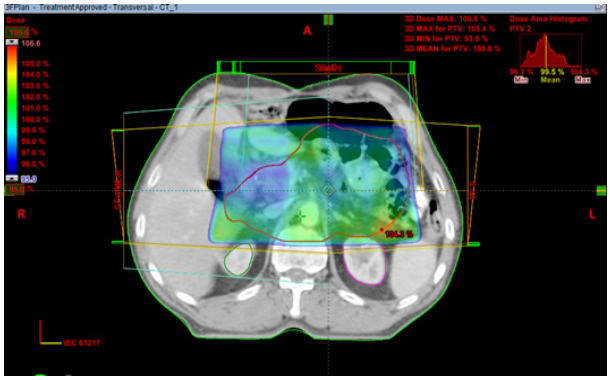

Figure 2. PTV with 95% Dose Colour Wash; 3DCRT Plan Showing Three Radiation Portals, Anterior; Right Lateral, and Left Lateral Fields

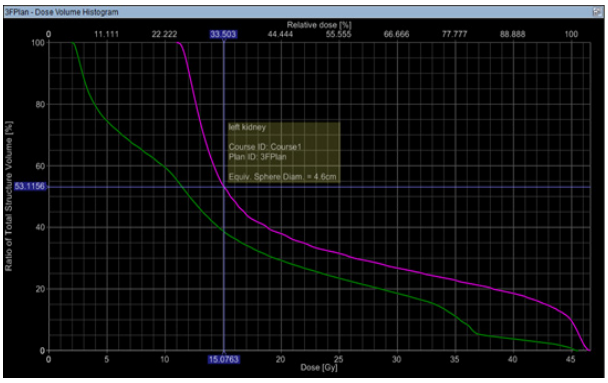

Figure 3. Dose Volume Histogram Showing V15 for Left Kidney and Right Kidney

and V20 was 69.2±15.8%. D195cc for the bowel bag was 36.3±10.8Gy, Dmax was 48.7±1.4Gy, and V45 was 29.2±9.8%. Dmax for spinal cord was 30.0±10.8Gy. Dmean for the heart was 4.5±0.84Gy (Table 3).

Discussion

Partial or total gastrectomy along with the D1 or D2 lymph-node dissection is the mainstay of treatment in the management of stomach cancer. Loco-regional recurrence is the major problem in patients treated with surgery alone necessitating various attempts at improving survival using

Table 2. Dosimetric Parameters of the Planning Target Volume (PTV)

PTV	Mean ± Standard deviation	Range
Volume[a]	848.6 ± 337.0	338 - 2610
Dmean[b]	45.2 ± 0.8	41.3 - 47.0
D98[b,c]	42.9 ± 1.0	39.1 - 44.6
D95[b]	43.4 ± 0.8	39.5 - 44.8
D50[b]	45.2 ± 0.7	41.8 - 47.3
D5[b]	47.3 ± 1.0	44.8 - 49.7
D2[b]	47.7 ± 1.1	45.6 - 50.7
Confomity index (CI)	1.23 ± 0.43	0.70 - 2.30
Homogenity index(HI)	1.09 ± 0.03	1.04 - 1.20

[a]PTV volume in cm^3; [b]Dose measured in Gray (Gy); [c]D98 is dose received by 98% of the PTV

Table 3. Dosimetric Parameters of the OARs

Organ at risk	Mean ± Standard deviation	Range
Right kidney		
Dmeana	11.9 ± 5.1	2.2 - 22.8
V18[b]	21.5 ± 13.8	0 - 55
V15	27.2 ± 14.9	0 - 61
V13	31.7 ± 15.7	0 - 65
Left kidney		
Dmean[a]	17.7 ± 5.8	8.5 - 45.6
V18[b]	33.5 ± 13.8	5.7 - 61.0
V15	43.2 ± 15.5	13.5 - 84.0
V13	59.0 ± 15.6	21.6 - 85
Heart		
Dmean[a]	4.5 ± 0.84	3.7 - 8.5
Liver		
Dmean[a]	27.7 ± 6.4	9.0 - 39.9
V20	69.2± 15.8	27 - 95
Bowel Bag		
Dmax[a]	48.7 ±1.4	44.7 - 52
V45	29.2±9.8	13.5 - 58.8
D195cc[a]	36.3±6.7	23.9 - 48.0
Spinal cord		
Dmax[a]	30.0 ±10.8	Jul-48

[a]Dose measured in Gray (Gy); [b]V18 is volume received by 18Gy in percentage

radiotherapy and chemotherapy both before and after surgery [5-11]. Adjuvant CRT became the standard of care since the introduction of SWOG/INT0116 trial [6]. The presence of OARs like spinal cord, liver, small bowel and bilateral kidneys limit the delivery of radiation dose to the post-operative tumour bed, especially with 2D-conformal radiotherapy where antero-posterior and postero-anterior (AP-PA) radiation portals were used. The high rates of Grade 3 toxicities seen in this seminal trial were subsequently minimized with the replacement of conventional treatment techniques by 3D-CRT and IMRT. With the introduction of 3D-CRT, dose to the OARs could be minimized with adequate delivery of dose to the tumour bed and nodal basin [4-12].

In our study, by using the standard RTOG tools, both HI and CI were within the range of reported IMRT data [13]. In a study by Li Z et al, the author compared dosimetric parameters of 5 field intensity-modulated radiotherapy (5F-IMRT), 7F-IMRT, single-arc volumetric modulated arc therapy (SA-VMAT) and double arc (DA)-VMAT [12]. All plans were made with the prescription dose of 50.4 Gy in 28 fractions. CI was 0.86±0.02 in both 5F-IMRT and 7F-IMRT planning's, 0.83±0.03 for SA-VMAT, and 0.87±0.03 for DA-VMAT planning. CI was better with the IMRT and ARC therapy compared to 3D-CRT planning in the current study due to the forward planning of 3D-CRT.

Kidney is a radiosensitive organ and abdominal or pelvic radiotherapy leads to damage to one or both the kidneys [14]. For bilateral kidneys, V20 <32%, mean dose < 15-18Gy, V12 <55% is recommended to get <5% of radiation induced kidney damage [15-16]. In the present study, mean dose to the left kidney was higher than the right kidney, the primary reason being that the left kidney in most of the patients was located within the target volume and tumor bed was anterior to the left kidney. However, the doses were comparable to that reported in various studies as outlined in Table 4 by both IMRT and 3D-CRT. Therefore, location of the post-operative bed rather than the technique appeared to be the primary limiting factor. Alani et al. defined separate high and low dose kidney instead of laterality to incorporate this concept.

Liver is a parallel organ, and the radiation induced liver damage (RILD) is found to correlate with the volume and dose of radiation received by the normal liver tissue. The incidence of RILD is dependent on the mean dose to the normal liver tissue with models predicting no cases of RILD with a mean liver dose < 31 Gy [20]. In the present study, mean dose to the liver was 27.7±6.4 Gy and V20 was 69.2±15.8 which were within the tolerable limit for the normal liver tissue. Though mean doses to the liver were lower with IMRT as reported by Li Z et al [12] and Minn et al. [8], 3D-CRT planning yielded values well within tolerance limits.

Severe gastro-intestinal (GI) toxicities are the main dose limiting factor in case of abdominal irradiation. In a comparison study of IMRT and 3D-CRT for adjuvant treatment of gastric cancer by Minn AY et al, grade 2 or higher GI toxicity was found to be similar between IMRT and 3D-CRT patients (61.2% and 61.5% respectively) and V45 for the bowel space is 106.2 cc, Dmax is 50.5 Gy for IMRT planning [18]. In another study by Liu GF et al, acute GI toxicities were found to be 56% and 54% for IMRT and 3D-CRT respectively [21]. Li Z et al showed that the Dmean for small intestine was 17.19±6.26 Gy for 5F-IMRT, 16.50±5.76 Gy for 7F-IMRT, 18.01±6.34 Gy for SA-VMAT, 16.90±5.92 Gy for DA-VMAT [13].

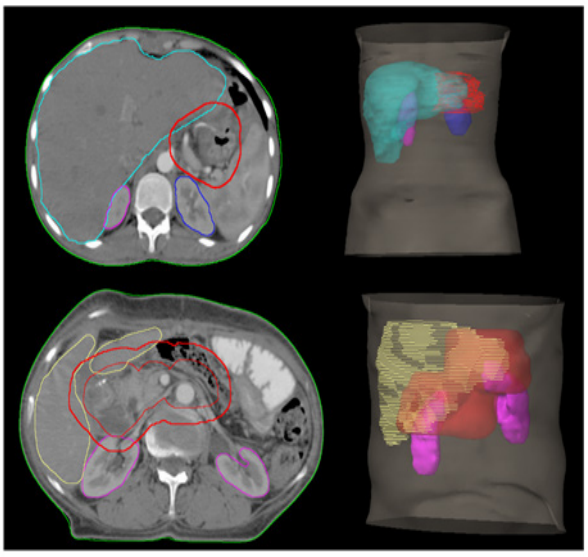

Figure 4. Position of CTV and OARs

In the present study, Dmax for the bowel bag is 48.7±1.4 Gy, V45 is 29.2±9.8%, and D195cc is 36.3±6.7 Gy which showed that the doses were comparable to the above mentioned studies.

For individual patients more than the radiotherapy technique it was the position of the anastomotic site which influenced high OAR doses (kidney and liver). The anastomotic sites and DVHs comparing kidney doses of an individual patient are shown in Figure 4.

Limitation of the current study are its retrospective nature and there is no direct comparison of 3D-CRT planning with the IMRT planning for the same set of patients.

In conclusion, results of the study suggest that there is a challenge in achieving the Organ at Risk (OAR) constraints in respect to bowel bag and mean doses achieved for left kidney in patients who had undergone D1 lymphadenectomy. It was also observed that inclusion of postoperative site was having changing position depending upon patient to patient which further led to difficulty in achieving constraints. Some of these patients may favour IMRT based treatment to have better dose delivery.

In the current study we found that post-operative 3D-CRT in cases of carcinoma stomach is acceptable in terms of target volume coverage and homogeneity. The strength of our current study is that it contains detailed dosimetric analysis in terms of physical parameters of target volume, HI, CI and OAR doses in a homogenous group of post-operative cases of carcinoma of stomach. In a country like India where we have increased patient load, we can spend less time on machine using 3D-CRT. Based on the result we could conclude that 3D-CRT offers good coverage of target volumes at the same time sparing the critical surrounding organs.

Table 4. Table Showing a Comparison between 3D-CRT and IMRT Plans of Bilateral Kidney Doses

		Current study (45 Gy)	Zhiping et al. (50.4 Gy) [12]		Alani et al. (45 Gy) [9]		Milano et al. (50.4 Gy) [17]		Zhang et al. (45 Gy) [18]		KK Murthy et al. (45 Gy) [19]	
		3D-CRT	5F-IMRT	7F-IMRT	3D-CRT	IMRT	3F	IMRT	3D-CRT	IMRT	4F-CRT	IMRT
Right kidney	Dmean	11.9±5.1	12.83±2.15	12.83±2.03	25.6 (High Dose Kidney)	12.8 (High Dose Kidney)	13.45	9.52	11.9±1.4	13.5 ± 0.65	12.0 ± 2.6	12.9 ± 2.5
	V18/V20	21.5±13.8	0.19±0.06	0.23±0.04	39	17			19.2 ± 1.1	16.2 ± 1.1		
Left kidney	Dmean	17.7±5.8	15.42±1.93	14.96±1.91	21.2 (Low Dose Kidney)	11.3 (Low Dose Kidney)	23.8	19.35	13.2 ± 1.21	15.3 ± 0.63	13.7 ± 3.1	15.0 ± 2.6
	V18/V20	33.5±13.8	0.27±0.04	0.28±0.04	17	7			29.9 ± 2.5	27.7 ± 1.8		

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RESEARCH ARTICLE

Frequency of Oral Sub Mucous Fibrosis and Its Correlation with the Level of Education in Patients Coming to a Tertiary Care Hospital of Karachi from January 2018 to December 2018

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Abstract

Objective: To determine the frequency of oral submucous fibrosis in patients coming to dental OPD of a tertiary care hospital and to correlate the association of level of education among patients of oral submucous fibrosis. **Methodology:** A cross sectional study was conducted from January 2018 to December 2018 among patients coming to the dental OPD of a tertiary care hospital in Karachi. Convenience sampling was used to select patients of Oral Submucous Fibrosis and a structured questionnaire was used to collect data on level of education, age, gender and Habit. **Result:** A total of 4405 patients visited the OPD and 135 patients were diagnosed with OSMF based on clinical findings. Mean age of OSMF patients was 33.6 years with nearly half 47.7% having no formal education.43.2% were skilled workers followed by 34.8% housewives and 22% were professionals. Betel nut was the most common used habit 79.5% among OSMF patients. Significant association of betelnut (p-0.001) among females(94.5%) compared to males (68.8%) and significant association of gutka (p-0.004) among males(24.7%) than females (5.5%)was observed. No significant association of level of education with substance abuse was observed. **Conclusion:** The finding of high frequency of betel nut usage among housewives and gutka among skilled workers is alarm some. Our literacy level despite being very low is not the sole reason of increase of substance abuse rather even the educated ones are not at par with this habit.

Keywords: OSMF- Karachi Pakistan- level of education- frequency

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Introduction

Oral submucous fibrosis is recognized by WHO as a precancerous lesion, which has a high rate of conversion into oral squamous cell carcinoma. The oral epithelium becomes atrophic and is injured easily along with fibrosis occurring in the tissue which limits the mouth opening. Problem gets much worst when the limitation increases to the level of inability of chewing and swallowing due to the fibrosis of the soft palate [1].

The disease is more prevalent in South East Asia whereas only few cases have been reported in the United States and European countries and those too are a result of the migratory Asians. Countries with the highest burden of disease are India, Taiwan, Srilanka and Pakistan. Studies done in India (Ahmadabad, Gujarat and other cities) have clear data on the increase in the incidence of oral cancer in the past 2 decades attributed to increase in the OSF cases. Largest increase of >30 times in the incidence of mouth cancer has been reported from 1985 to 2010 [2].

Studies indicated that men are most commonly affected between the ages of 25-35 in both rural and urban population [2].

Studies conducted in various parts of South East Asia have established betel nut (areca nut) as the major risk factor of OSF. Betel nut (areca nut) chewing directly or in the form of pan, gutka or mawa has been reported to cause OSF. (100% among OSF cases in Taiwan) [3]. The International Agency for Research on cancer of the

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WHO evaluated areca nut as a carcinogenic substance [4]. OSF is related to both its frequency of usage and duration that it's kept in the mouth. A survey was conducted in different socioeconomic areas to assess the knowledge of people regarding the adverse effects of betel nut which concluded that despite having knowledge about oral cancer people were reluctant to give away the habit. [5]. The billion dollar market of gutka with easy access and reduced price and the increasing incidence of OSF, constitutes a major public health risk with young being the most vulnerable [2]. However there has been no research to find out if the level of education can reduce the habit of substance abuse, resulting in reduction of Oral Submucous Fibrosis. The objective of the study is to determine the frequency of Oral Submucous Fibrosis in patients coming to dental OPD of Sindh Institute of Oral Health Sciences from January 2018 to December 2018 and to compare the level of education among patients of oral submucous Fibrosis.

Materials and Methods

A cross sectional study was conducted from January 2018 to December 2018 in patients coming to the dental OPD of Sindh Institute of Oral Health Sciences. Convenience sampling was used to select cases of oral Submucous Fibrosis. Inclusion criteria was all subjects diagnosed on basis of presence of fibrous bands causing decreased mouth opening (<30mm) were included in the study. Fibrous bands were palpated through clinical examination and mouth opening measured with vernier caliper. For the collection of data, a structured questionnaire containing details of socio-demographic, habit characteristics and level of education was used.

SPSS 20 was used for data analysis. Qualitative variables were summarized as percentages and quantitative variables as mean and standard deviation. Chi- square test was used to determine the relation between independent factors (age, gender, occupation and Habit (form, frequency and duration) with dependent factor i.e. level of education among oral submucous Fibrosis patients. P-value of < 0.05 was considered significant. Ethical approval was taken from the institutional review board and informed consent was obtained from all participants. Data was collected by trained data collectors and supervised by the principal Investigator.

Results

A total of 4405 patients visited the dental OPD from January 2018 to December 2018. Around 135 cases of oral submucous Fibrosis were identified out of 4405 based on clinical presentation of Fibrous bands and limited mouth opening. 2% of the participants did not consent to participate in the study which left the sample to be 132 cases of OSMF.

More than half of the patients with oral submucous fibrosis were males 58.3% (77) followed by 41.7% (55) females. The mean age of the patients was 33.64 (SD 12.58). Nearly half of the patients had no formal education 47.7% (63) and only one third had primary and matric 27.3% (36) and intermediate and above 25% (33). Nearly half of the patients were skilled workers (laborers, carpenters, street wanders and construction workers) 43.2% (57) followed by 34.8% (46) housewives and 22% (29) professionals (doctors, nurses, businessman, and engineers) (Table 1).

Table 1. Sociodemographic Characteristics of Patients with OSF (n=132)

Variables	%/n & Mean (SD)
Gender	
Males	58.3% (77)
Females	41.7% (55)
Age	33.64 (SD 12.58)
Education	
No Formal Education	47.7% (63)
Primary and Matric	27.3% (36)
Intermediate and Above	25% (33)
Occupation	
Housewives	34.8% (46)
Skilled	43.2% (57)
Professional	22% (29)

As shown in (Figure 1) more than three –forth (3/4) 79.5% of the patients ate Betel nut (betel nut), while 22% ate Pan, 16.7% Gutka and 6.8% did smoking.

The average daily consumption of Betel nut in patients of oral submucous Fibrosis was 6.10 (SD 3.9) packets and the average mean duration of use is 9.09 (SD 5.3) years. The average daily consumption of Pan is 5.5 (Standard deviation of (SD) 5.2) and average years consumed is 10.41 (SD 5.6) in patients of oral submucous fibrosis. The mean daily consumption of Gutka is 3.41 (SD 2.1) and average years consumed is 9.09 (SD 6.3). Whereas the average cigarettes smoked is 9 (SD 7.3) per day in patients of oral submucous fibrosis and the average years consumed is 11.78 (SD 3.4) (Table-2)

As shown in Table 3 When different substances were compared with independent factors we found a significant association (p-value 0.001) of Betel nut with females showing higher frequency (94.5%) as compared to males

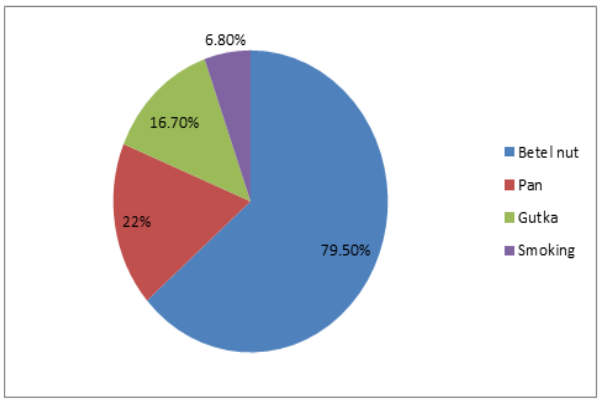

Figure 1. Frequency of Different Substance Abuse among Oral Submucous Fibrosis Patients (n=132)

Table 2. Daily Consumption and Duration of Use of Different Substance Abuse among Oral Submucous Fibrosis Patients (n=132)

Habits	Daily comsumption Mean (SD)	Duration (Years) of use-Mean (SD)
Betel nut	6.10 (3.9)	9.09 (5.3)
Pan	5.5(5.2)	10.41 (5.6)
Gutka	3.41 (2.1)	9.09 (6.3)
Smoking	9 (7.3)	11.78 (3.4)

Table 3. Comparison of Frequency of Substance Abuse with Different Factors

Variables	Frequency of Betel nut	p-value	Frequency of Pan	p-value	Frequency of Gutka	p-value	Frequency of Smoking	p-value
Gender								
Male	68.80%	0.001	24.70%	0.374	24.70%	0.004	11.70%	0.01
Female	94.50%		18.20%		5.50%		1%	
Education								
No formal education	79.40%	0.598	19%	0.579	12.70%	0.111	9.50%	0.458
Primary and Matric	75%		27.80%		27.80%		5.60%	
Intermediate and Above	84.80%		21.20%		12.10%		3%	
Occupation								
Housewife	93.50%	0.001	19.60%	0.283	6.50%	0.002	1%	0.014
Skilled	63.20%		28.10%		29.80%		14%	
Professional	89.70%		13.80%		6.90%		3.40%	

(68.8%). Also a significant association (p-value 0.004) was observed in the frequency of Gutka consumption with Males (24.7%) consuming higher frequency than females (5.5%). The association of Gender with smoking was also significant (p-value 0.010) with males (11.7%) as compared to females (1%). The level of Education had no significant association with any of the substance abuse. Occupation was significantly associated (p-value 0.001) with frequency of Betel nut in housewives (93.5%) as compared to Skilled (63.2%) and Professionals (89.7%). Occupation was also significantly associated (p-value 0.002) with gutka more consumed among Skilled (29.8%) as compared to housewives (6.5%) and (6.9%) in professionals. Skilled workers (14%) also showed more frequency in smoking as compared to housewives (1%) and professionals (3.4%) and the association was significant (p-value 0.014).

Discussion

The frequency of Oral Submucous Fibrosis was found to be 3% in patients coming to dental OPD within one year. The frequency is higher than was observed in Dhanbad district of Jharkand, India which was found to be 1% in 2018 [6]. But is consistent with findings from Hunain Province, China 1%-3% [7]. Majority of the patients were males with an average age of 33 years, which is consistent with studies from the Asian sub-continent and also a previous study conducted in Pakistan by Sidra Mohiuddin [6-8]

We found that majority of the patients of OSMF consume betel nut 79.5% on daily basis with an average consumption of 6 packets daily for nine years. This is consistent with the study from Taiwan and India which clearly states the use of betel nut as a major etiological factor for OSMF [2-3]. However a large number of Gutka consumers 16.7% (also a product of betel quid and slime) are associated with increased of OSMF and the second major habit found in our study is the use of Gutka among OSMF patients [9]. According the Pakistan Medical association's statistics 1.5 million oral cancers occur due to the use of betel quid and gutka [13].

The use of betel nut was significantly higher in females as compared to males in our study and this finding is in contrast to previous studies conducted in Pakistan and India [1-10] which shows a high frequency among men, however our results are in line with study in Cambodia and Pacific island of Palau where women are predominant users of Betel nut [11-12]. Also the rare use of female smoking observed in our study is consistent with Cambodia [14], where a significantly low usage is observed among females than males. However the use of gutka is more among males which is also in line with previous studies [9-13].

We found that the Habits of betel nut, gutka, pan and smoking were more among those who had no formal education which is in contrast to study in India where high frequency was observed among Secondary and college students followed by illiterate [14]. However the use of gutka among skilled workers is in line with studies from India which also highlights the use of gutka and betel nut among laborers, tea sellers, wage earners and other skilled workers as compared to professionals like engineers, managers and other formally employed workers [14]. A major reason is the need of alertness and reduced hunger which these products are known to provide along

with their soothing effects, which is a major compromise in low-income countries substituting low cost substance abuse with healthy diet [14]. However the high usage of betel nut among housewives is very much related to the familial background of consumption as highlighted in previous literature [9-14].

No association of habit with education clearly states that there is a need of awareness campaigns at school and college levels which would reduce the menace among the educated class. Also we recommend provision of low cost healthy food to the skilled and daily earners, so they won't have to kill their hunger in order to survive and rely on such substances of abuse. Moreover strict action of government is required in the commercial ban of the product with regular monitoring and follow-up.

We had limitations and the study was only a single government hospital, therefore the results cannot be generalized on the entire population of Karachi.

In conclusion, the study is only a snap shot of the current patients of OSMF coming to dental OPD of a tertiary care hospital. The finding of high frequency of betel nut usage among housewives and gutka among skilled workers is alarm some. Our literacy level despite being very low is not the sole reason of increase of substance abuse rather even the educated ones are not at par with this habit.

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RESEARCH ARTICLE

Mongolian Breast Cancer Incidence: A Follow-up Report

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Abstract

Objective: Understanding variance in global breast cancer incidence rates may help identify risk factors and could lead to increased efforts for prevention. In our previous study on breast cancer in Mongolia from 1998-2005, we reported that the incidence of breast cancer, though on the rise, remains lower in Mongolia than in adjacent Asian countries. Through the addition of almost a decade of data (2006-2014), we provide a study update and describe trends in breast cancer incidence and staging distributions within Mongolia, with further analyses examining women in urban and rural regions. **Methods:** Age-standardized breast cancer incidence and staging distributions were obtained from the Mongolian National Oncology Center and were used to describe trends in cancer over time. **Results:** Our findings indicate that the overall incidence of breast cancer has continued to increase in Mongolia, with rural women still experiencing lower risk than their urban counterparts. Given similarities in cancer staging, the observed geographic variation does not appear to result from differences in cancer stage at diagnosis over time or by region. **Conclusions:** Considering the variation in rural and urban populations, data from this study could be used to better understand the influence of westernization on cancer risk in Asian countries and beyond. Further research on demographic shifts in breast cancer incidence within Mongolia may elucidate novel risk factors explaining variations active among other populations.

Keywords: Breast cancer- urban-rural- Asia- international- cancer staging

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Introduction

Breast cancer is a leading cause of mortality in women in developed and developing countries around the world. While Asia is responsible for a large proportion of the global burden of cancer, breast cancer rates across the continent have been historically low in comparison with more westernized countries [1]. The incidence and mortality rates of breast cancer in Mongolia are lower than in other Asian countries, at 8.0 per 1,000 [1]. However, rates have been steadily increasing on an annual basis and vary by geographic regions, with the highest incidence rates in the most urban districts [2]. A similar urban-rural difference has been reported in other Asian countries, engendering questions about the potential long-term impacts of westernization and lifestyle change on health [3].

In our previous study analyzing breast cancer rates in Mongolia from 1998 to 2005, we reported that the incidence of breast cancer, though on the rise, remained lower in Mongolia than in other Asian countries [4]. Since our original paper was published, other studies describing similar trends have raised concerns about the growing cancer risk for the region. Using registry data from 2009-2013, researchers identified a substantial and consistent increase in breast cancer, supporting the trend that was first described in our original paper [4].

Other studies have considered the implications of an increasing prevalence of breast cancer by studying shifts in survival rates. Although cancer survival data is limited, emerging evidence suggests that most breast cancers in Mongolia are diagnosed at a late stage, as the 5-year breast cancer survival rate is considerably lower than that observed in more westernized countries [5-6]. Since mammography screening is known to reduce breast cancer mortality in Western countries, the lack of

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a population-based screening program in Mongolia is of interest to researchers and clinicians. According to recently published national guidelines, breast screening is not currently instituted in Mongolia due to its low relative incidence compared to other cancers and limited resources [7]. Consequently, Mongolian women predominantly rely on self-screening and routine clinical exams to detect breast cancers. As a potential result, Mongolian women are more likely to be clinically diagnosed with later-stage tumors, leading to an increased rate of mortality from breast cancer [4-6]. Although evidence has not yet been published, one possibility is that insufficient access to health services could contribute to a delay in diagnosis. Thus, we hypothesize that limited access to clinical exams in more remote regions of Mongolia could result in a higher risk of later-stage breast cancer among rural women.

As described in our original paper and supported by other recent epidemiological studies, geographic variations in breast cancer risk exist within Mongolia. We previously reported that the annual percent increase in breast cancer rates was higher in urban areas than in rural areas. We also found that breast cancer staging was similar across time and geographic groups, with most cases at stage III or IV at diagnosis [4]. Researchers have since proposed that risk factors associated with westernization such as lifestyle factors (e.g., diet, physical activity), breast density, and hormone levels could account for geographic variations in Mongolia, but more data are needed to comprehensively address these hypotheses [8].

Here we provide an update to our original study and analyze breast cancer trends in Mongolia through the addition of nearly a decade of cancer registry data (2006-2014). With the additional data, we describe variations in breast cancer risk and breast cancer staging within Mongolia, overall and for urban and rural populations over time. We present a more thorough analysis of incidence and risk that is crucial to understanding the burden of breast cancer in Mongolia. Given the demographic shift towards a more Western-influenced lifestyle among many Asian countries, temporal data from Mongolia could tell us more about the inherent biological changes and risks that result from increased urbanization.

Materials and Methods

We used annual age-specific breast cancer registry data available from the Mongolian National Oncology Center (NOC) to describe trends in the population from 1995 to 2014. In Mongolia, incident cancer cases are first reported to one of the 21 Mongolian aimags, provinces, and then submitted to the NOC. The NOC data are presented by geographical area and population density, allowing separate analyses of rates among rural-urban groups.

Using annual population data for each aimag, we calculated age-specific breast cancer incidence rates for women in 5-year age groups. Age-specific rates (i.e., the number of cases divided by the number of women in that age group) were then multiplied by the corresponding number of women in the World Standard Million. The World Standard Million is a standard population value calculated by the Surveillance, Epidemiology and End Results (SEER) program [9]. Each value was divided by the total number of women above the age of 20 in the World Standard Million. Products were summed across age groups for each calendar year and province and then multiplied by 100,000. In summary, we calculated a weighted average of the age-specific rates, weighing each rate by the corresponding fraction of the World Standard Million. We then analyzed the age-standardized rates by the calendar year of diagnosis, urban-rural residence, and breast cancer stage.

Results

Since the data from the NOC are presented by geographic areas and population density, it is important to understand population demographics for the country of Mongolia. Based on estimations for July 2020, Mongolia's population is about 3.2 million and is relatively young compared to other countries [10]. In 2019, 31.2% of the population was <15 years of age and 4.1% of the population was >65 years of age [11]. The median age of females in Mongolia was 30.7 years old and life expectancy for women in Mongolia is 75.2 years of age [10-11]. These values have changed since our previous publication, showing an increase in the overall population and an aging of the population.

Although many Mongolians live as nomads or semi-nomadic herdsmen, the population of Mongolia has experienced a recent shift in urbanization [10]. In 2019, approximately 67.8% of the population resided in urban areas, while in 2008, only 54.6% of the population were considered urban [4-11]. In our original paper, we reported that approximately 60% of the population lived in the capital city of Ulaanbaatar (UB), whereas in 2018, an estimated 46.1% of the population resided in UB [4-11]. As degrees of urbanization continue to change in Mongolia, the potential health effects of western lifestyles remain relevant and of increasing interest.

Based on our analyses, the updated data from the NOC indicate a steadily increasing incidence of breast cancer in Mongolia, further supporting the findings in our original paper. As shown in Figure 1, the updated rates indicate that the overall incidence of breast cancer has continued to increase in Mongolia, with rural women still experiencing a lower risk than urban women. These results support our earlier findings and suggest further research on demographic shifts in breast cancer incidence within Asia is necessary.

To address the hypothesis that greater access to clinical exams could lead to earlier diagnoses for urban women, we analyzed tumor staging by comparing the proportion of women diagnosed at each cancer stage from 1998 to 2014. As shown in Figure 2, breast cancer staging was found to be relatively consistent between women in urban and rural Mongolia. These results suggest that breast cancer staging distributions have not changed substantially over

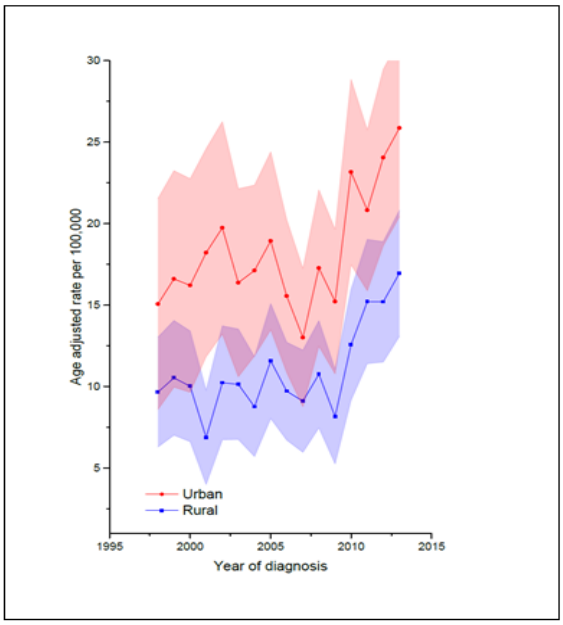

Figure 1. Age-standardized Breast Cancer Incidence Rates in Mongolia by Population (cases/100,00) from 1998-2014

time in Mongolia.

Discussion

Our findings indicate that the overall incidence of breast cancer has continued to increase in Mongolia, with rural women experiencing a lower cancer risk than their urban counterparts. While the overall prevalence of breast cancer screening in Mongolia is low compared to other countries, greater access to clinical breast screening examinations in urban areas could result in geographic differences in incidence [8-12]. Given Mongolia's demographic shifts and a steady increase in urbanization, the urban-rural incidence differences raise questions about the influence of westernization on breast-cancer risks.

Mongolia's high breast cancer mortality rate led us to consider that a lack of available routine mammographic screening could result in a higher prevalence of late-stage cancers in rural women. However, our results indicate that breast cancer staging was similar for cases in urban and rural women. For both groups, stage III accounted for the highest proportion of breast cancer cases while stage I accounted for the lowest proportion. This high prevalence of late-stage cancer is compatible with findings from other studies and perhaps reflects the absence of a national screening program, rather than regional differences [13]. Although we did not find a significant difference in cancer staging over time, evidence from other sources finds that staging has changed for many cancers in Mongolia. In 2018, Mongolia's Annual Health Report found that 76.1% of incident cancers were diagnosed at later stages, compared to 90% in 2008 [4-11].

Limitations of this report are like those that impacted our original study. Given the high tendency for back and forth migration over time in Mongolia, misclassification of women's residence as urban or rural could have occurred. However, unless women are systematically relocating to urban areas before a breast cancer diagnosis, the misclassification of residence concerning cancer would be considered random. Additionally, the completeness of the data could have affected our findings. Interviews with the individuals involved in the registry have led us to believe that cancer reporting in Mongolia is generally high. Since cancers may need to advance before being diagnosed, the accuracy and completeness of diagnoses are unknown. However,

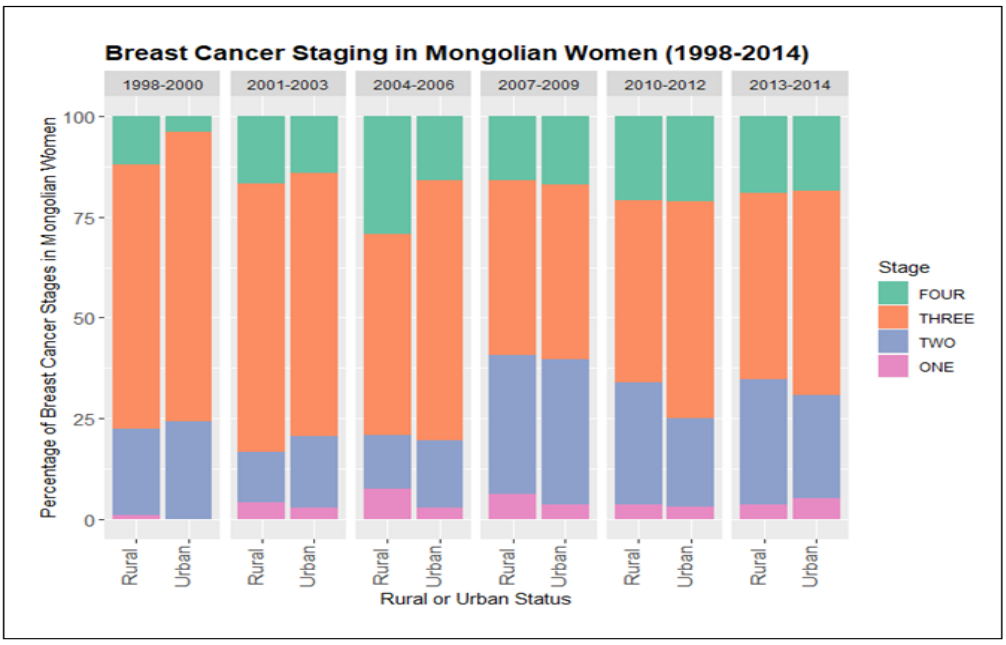

Figure 2. Breast Cancer Incidence by Percent Stage at Diagnosis for Mongolia from 1998-2014

the non-localized stage of many of the cancers suggests that advanced disease is being diagnosed and reported to the NOC.

The additional data included in this short report strengthens our previous observation that breast cancer incidence in Mongolia is increasing and remains higher in urban provinces than in rural regions. The differing urban and rural incidence rates could imply an emerging difference between women living in traditional settings and those moving to urban areas, offering a possible explanation for why breast cancer incidence rates vary between Mongolia and more westernized Asian countries. We conclude that further research on demographic shifts in breast cancer incidence within Asia should be considered, as it may elucidate novel cancer risk factors active among other populations.

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Statement of Conflict of Interest

The authors declare no conflict of interest.

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RESEARCH ARTICLE

Prevalence and Potential Factors Related to Irreversible Chemotherapy-induced Amenorrhea in Premenopausal Breast Cancer Patients

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Abstract

Objective: To evaluate the prevalence and potential factors related to irreversible chemotherapy-induced amenorrhea (CIA) in premenopausal women with breast cancer. **Methods:** First diagnosis breast cancer women in Stages I-III who had menstruation within three months before receiving chemotherapy and completed a course of treatment were interviewed about the menstrual cycle after a complete course of chemotherapy and the subsequent menstrual status. Clinical data were retrospectively reviewed. Age at starting chemotherapy was calculated for an optimal cut-off point by using the receiver operating characteristic curve to predict irreversible CIA. The clinicopathological variables were compared using univariate and multivariate analysis to identify the independent factors related to irreversible CIA. **Results:** One hundred and fifty-four premenopausal breast cancer women who met the inclusion criteria were interviewed. They were treated with chemotherapy between October 1999 and September 2018. The median age at the start of treatment was 43.5 years. One hundred forty-two patients (92.2%) developed CIA and 37 cases subsequently resumed menstruation (RM). Thus, the prevalence of irreversible CIA was 68.2%. The group > 45 years of age, estrogen receptor-positive, progesterone receptor-positive and maintenance treatment with tamoxifen significantly developed irreversible CIA in univariate analysis. However, only the > 45-year-old group was an independent factor for the CIA with an adjusted odds ratio of 23.04. **Conclusion:** Nearly 70% of premenopausal breast cancer women developed irreversible CIA and the independent factor for this event was being older than 45-years-old when receiving chemotherapy.

Keywords: Breast cancer- chemotherapy- amenorrhea

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Introduction

Breast cancer is the most common female cancer in the world with the age-standardized incidence rate (ASR) and mortality rate as high as 46.3 and 13.0 per 100,000 persons-year, respectively. In Thailand, breast cancer also ranks as the number one female cancer with the ASR as 34.4 per 100,000 people per year [1]. The principle treatment of breast cancer included surgery followed by adjuvant chemotherapy, radiotherapy or hormonal therapy depending on the stage and the specific receptors [2]. One major concern was the issue of breast cancer trending to occur in young aged women. Globocan 2018 reported ASR of breast cancer women younger than 45 years-old as 13.4 per 100,000 people per year [1]. In this age group, the cytotoxic chemotherapy used as adjuvant drugs for treating breast cancer such as doxorubicin, cyclophosphamide, docetaxel, paclitaxel, methotrexate, and 5-fluorouracil affected the ovarian function by destroying and eliminating the primordial follicles and subsequently induced transient or permanent amenorrhea [3]. These effects may result in physiological changes associated with menopausal problems like osteoporosis, hypercholesterolemia, hot flushes, genitourinary symptom, psychologic stress, weight gain and infertility [4]. Due to the prohibition for giving hormonal therapy to breast cancer survivors, the resuming of menstruation after discontinued chemotherapy is very important to reduce

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such problems. The incidence of chemotherapy-induced amenorrhea (CIA) from a previous report varied from 10% to 93% depending on the definition of CIA, the differences in follow up time and characteristics of patients in each study [5]. However, the rate of CIA and the prevalence of the resumption of menstruation (RM) in Thai premenopausal breast cancer patients is limited. Therefore, we conducted the current study to identify these data and the factors related to irreversible menstruation.

Materials and Methods

This prospective study was conducted after approval from the Ethics Committee of the Faculty of Medicine, Chiang Mai University. All newly diagnosed stage I-III breast cancer patients treated between October 1999 and September 2018 who had regular menstruation with the last menstrual period occurring within three months before starting chemotherapy and free of disease more than 12 months after a complete course of chemotherapy were invited to participate in this study. All of them communicated well in the Thai language and could respond to the well-trained interviewers regarding their history of menstruation after just finishing the first course of chemotherapy and the subsequent menstrual status. The interview process was conducted at the Outpatient Department of Surgery when the patients came to follow up after completing their treatment. All eligible patients gave informed consent before participation in this project. Patients who developed bilateral breast cancer, previous hysterectomy, received GnRH analog and could not provide their menstrual history were not included in the study. The demographic data, the breast cancer characteristics and the details of the anti-cancer treatment of all participants were reviewed and recorded. We defined the CIA as amenorrhea for longer than or equal to three months. The resumption of menstruation was defined as at least two cycles of menstruation bleeding after CIA.

The sample size for this trial was estimated on the basis of a prior study that revealed 90% of premenopausal women developed CIA [6]. The 95 inter-percentile reference intervals for calculation accommodated the possibility of a loss of follow up participants. Finally, this study needed to enroll about 150 participants.

Statistical analysis of the data was carried out using the IBM SPSS Statistics for Windows program (Version 22). Descriptive statistics were used to summarize patient characteristics and menstrual history. Chi-square or Fisher's exact test was used for comparative analysis of the factors between irreversible CIA and resuming of menstruation groups to calculate the odds ratio of categorical variables. A receiver operating characteristic curve (ROC) was used to assess the discriminative value and the best cut-off value of the possible factors was determined to further predict the irreversible CIA. Binary logistic regression analysis with an enter method was used to identify the potential independent predictive factors for continuous CIA. A p-value of < 0.05 was considered statistically significant.

Results

One hundred and fifty-four patients who met the inclusion criteria were interviewed in the study period. The median age at the interviewed time and at the time of receiving chemotherapy was 49 and 43.5 years old, respectively. The median time from completed first-line chemotherapy to study entry was four years with a range of 1-20 years. The mean body mass index was 23.87 kg/m^2 and the median tumor size was 2.5 cm. About 40% of the studied patients did not use any contraception before starting chemotherapy while 20% of them used oral contraceptive pills. The most common histology was invasive ductal carcinoma and about 72% presented with positive estrogen receptor (ER) and tamoxifen was given in three-fourths of the patients. Nearly 90% were still free of disease at the interview time. The details of the clinical data were noted in Table 1.

The type of chemotherapy was presented in Table 2. The three most frequent regimens were fluorouracil+ adriamycin+cyclophosphamide (FAC), Adriamycin plus cyclophosphamide (AC) and AC followed by paclitaxel.

Regarding menstruation status, 142 patients (92.2%) developed the CIA after completing first-line chemotherapy while 12 cases still had menstruation while receiving chemotherapy. However, 37 cases of the CIA patients (35.2%) resumed normal menstruation indicating that 68.2% of these participants developed irreversible CIA.

To identify the independent factors related to the resumption of menstruation by using the ROC curve, only age at the cut-off point of 45 years old was the potential factor as shown in Figure 1. Furthermore, Table 3 demonstrated the significant factors that might predict irreversible CIA. The results showed that the age group older or equal to 45 years, ER-positive,

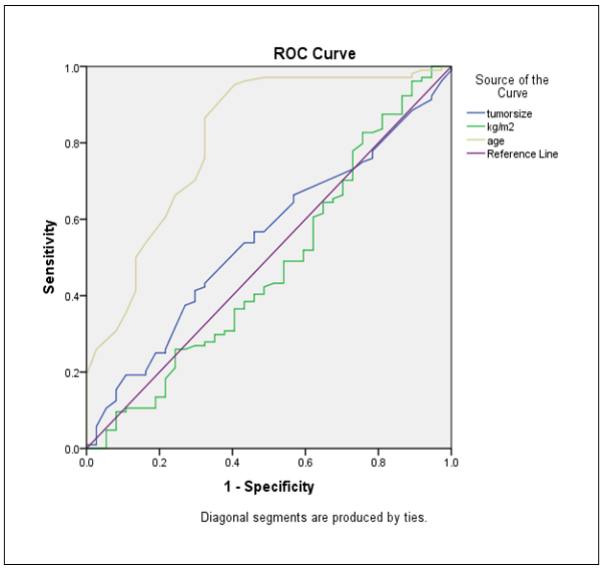

Figure 1. Receiver-Operating-Characteristic (ROC) and Area Under the Curve (AUC) for Clinical Characteristics to Predict Chemotherapy-Induced Amenorrhea.
Test, Age; AUC, 0.812; 95% CI, 0.726-0.899; Cut-off Point, 45; Sensitivity, 0.865; Specificity, 0.324; P-Value, < 0.001

Table 1. Clinical Characteristics N = 154

Median age of interviewed (range: year)	49 (24-65)
Median age of received chemotherapy (range: year)	43.5 (23-55)
Mean BMI (SD: kg/m^2)	23.87 (3.90)
Median tumor size (range: cm)	2.5 (0.9-11.0)
Last contraception (before chemotherapy began) (%)	
Oral contraceptive pill	32 (20.8)
Depo- Medroxy Progesterone Acetate (DMPA)	6 (3.9)
Intrauterine device	2 (1.3)
Tubal resection	34 (22.1)
Condom	6 (3.9)
Coitus interruptus	10 (6.5)
None	64 (41.6)
FIGO staging (%)	
IA	35 (22.7)
IB	1 (0.6)
IIA	67 (43.5)
IIB	25 (16.2)
IIC	1 (0.6)
IIIA	21 (13.6)
IIIB	1 (0.6)
IIIC	3 (1.9)
Histology (%)	
Ductal carcinoma in situ (DCIS)	2 (1.3)
Ductal carcinoma	1 (0.6)
Encapsulated papillary carcinoma	1 (0.6)
Invasive ductal carcinoma (IDCA)	135 (87.7)
Invasive lobular carcinoma	3 (1.9)
Invasive papillary carcinoma	2 (1.2)
Micropapillary carcinoma	1 (0.6)
Mixed mucinous with IDCA	1 (0.6)
Mucinous carcinoma	7 (4.5)
Tubular carcinoma	1 (0.6)
Menstrual status after completed 1st line chemotherapy course (%)	
Irreversible amenorrhea	105 (68.2)
Resumed menstruation	37 (24.0)
Ongoing menstruation	12 (7.8)
Current status of menstruation (interview day) (%)	
Amenorrhea	118 (76.6)
Normal menstruation	36 (23.4)
Receptor positive (%)	
Estrogen	112 (72.7)
Progesterone	105 (31.8)
Human epidermal growth factor receptor 2 (HER2)	37 (24.0)
Received tamoxifen (%)	116 (75.3)
Current status (%)	
Free of disease	125 (88.0)
Recurrence	15 (10.6)
Developed other malignancy	2 (1.4)

progesterone receptor (PR) positive and tamoxifen usage were significant in univariate analysis while only the group older or equal to 45 years old was significant in multivariate analysis. Thus, the age group over or equal to 45 years old was an independent factor related to CIA.

Table 4 summarizes 12 patients who still had menstruation while receiving chemotherapy. Their range age was between 23 and 47 years old and ten patients continued normal menstruation while two patients were in menopause at the interviewing time. All these patients received cyclophosphamide combined with other chemotherapy such as adriamycin, fluorouracil, paclitaxel, etc. All except two patients were still free of disease at the interview time while each the remainder developed a recurrent and second malignancy.

Discussion

The rate of CIA in breast cancer patients who received first-line chemotherapy in the present study was 92.2% and 35.2 % of them resumed menstruation while 7.8% of all participants still developed menstruation during and after receiving chemotherapy. This prevalence rate was similar to a previous publication from Japan. Kota et al. [7] studied menstruation in 101 premenopausal Stage I-III hormonal receptor-positive Japanese breast cancer women who received chemotherapy. The authors defined CIA as the disappearance of periodic menstruation during chemotherapy and if the menstruation appeared after finishing the course of chemotherapy, this state was defined as a resumption of menstruation. CIA in their study was 96% and about 40% of them resumed menstruation with a variation of 1-3 years depending on the age. All patients less than 30 years of age resumed menstruation within one year while 60% of patients aged more than 35-year-old resumed menstruation around 2-3 years. Another study from China, Liem et al [6], reported the rate of CIA in premenopausal breast cancer women aged less than 45-year-old as 91% and the rate of resumption of menstruation of 66.7%. The definition of CIA in this study was amenorrhea more than three months while receiving chemotherapy or within 12 months after completion of

Table 2. Chemotherapy Regimen

Regimen	N (%)
AC	38 (24.6)
AC + T	39 (25.3)
AC+ TH	6 (3.8)
FAC	44 (28.6)
FEC	7 (4.5)
CMF	6 (3.9)
FAC+T	5 (3.2)
Other*	9 (5.8)

*Other, AC + FAC + AC + TH (1), CMF + AC (1), FAC + AC (1), FAC + TH (1), FEC + D (2), FEC + T (1), FEC + TH (1), TC (1); AC; Adriamycin + cyclophosphamide, FAC; fluouracil + Adriamycin + cyclophosphamide, FEC; fluouracil + epirubicin + cyclophosphamide, MF; cyclophosphamide + methotrexate, fluorouracil, T; paclitaxel, TH; trastuzumab (Herceptin)'D; docetaxel

Table 3. Factors to Predict Chemotherapy-Induced Amenorrhea

Factors	Number of Patients Divided by Menstrual Status		Total	Univariate Analysis*		Multivariate Analysis†	
	CIA (%)	RM (%)	(%)	OD (95% CI)	P- Value	Adjusted OR (95% CI)	P- Value
Age > 45 years	57 (40.1)	2 (1.4)	59 (41.5)	20.781	< 0.001	23.041	< 0.001
Age < 45 years	48 (57.8)	35 (24.6)	83 (58.5)	(4.751-90.906)			
ER					0.026	1.724	0.685
Positive	85 (59.9)	23 (16.2)	108 (76.1)	2.587			
Negative	20 (14.1)	14 (9.9)	34 (23.9)	(1.135-5.896)			
PR					0.005	2.521	0.253
Positive	82 (57.7)	20 (14.1)	102 (71.8)	3.03			
Negative	23 (16.2)	17 (12.0)	40 (28.2)	(1.369-6.710)			
HER2	24 (16.9)	11 (7.7)	35 (24.6)	0.7	0.404	0.981	0.973
Positive	81 (57.0)	26 (18.3)	107 (75.4)	(0.303-1.621)			
Negative#							
Tamoxifen	88 (62.0)	24 (16.9)	112 (78.9)	2.804	0.015	0.518	0.675
Yes	17 (12.0)	13 (9.2)	30 (21.1)	(1.197-6.571)			
No							
Stage					0.124	0.372	0.095
I	21 (14.8)	12 (8.5)	33 (23.2)	0.521			
II&III	84 (59.2)	25 (17.6)	109 (76.8)	(0.225-1.204)			
Chemotherapy					0.867	0.811	0.729
AC regimen	27 (19.0)	9 (6.3)	36 (25.4)	1.077			
Other	78 (54.9)	28 (19.7)	106 (74.6)	(0.452-2.569)			
Lasted contraception				0.935	0.876	0.944	0.91
Hormone-relatedd	27 (19.0)	10 (7.0)	37 (26.1)	(0.401-2.181)			
Non-hormone related							
	78 (54.9)	27 (19.0)	105 (73.9)				
Response	95 (66.9)	32 (22.5)	127 (89.4)	1.484	0.497	1.308	0.687
No recurrence	10 (7.0)	5 (3.5)	15 (10.6)	(0.472-4.668)			
Recurrence							

*chi-square test; †Binary regression analysis (Enter); CIA, chemotherapy induced amenorrhea; RM, resumed menstruation; OR, odds ratio; 95% CI, 95% confidence interval; ER ,estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; AC, Adriamycin + cyclophosphamide; # Equivocal, 25 cases.

chemotherapy while the resumption of menstruation was defined as at least two cycles of menstruation after CIA. Their results corresponded to our study except for the rate of resumption of menstruation. Our study found the rate of resume menstruation only 24.6% in patients younger than 45 years old. This difference might be from the variant of the number of participants and the chemotherapy regimens. Moreover, Shin et al. [8] recently reported the rate of CIA in 237 premenopausal Korean breast cancer women aged 20-44 years who treated with chemotherapy after surgery. They found the rate of CIA as 61.6% and the rate of irreversible CIA was 13.1% at one year. Due to the varied rate of CIA in various publications, Zavos and Valachis [9] performed meta-analysis from 75 studies that presented the data of CIA and found that the pooled rate of CIA was 55% and the rate of CIA was increased by age. The authors summarized both ages more than 40-year-old and the use of tamoxifen were the risk factors for developing CIA.

Regarding independent factors related to CIA, our study revealed only age older than 45 years-old impacted irreversible CIA. This result was similar to previous reports that showed younger ages related to the resumption of menstruation [6-10]. However, Meng et al. [10] published their study about this issue in 73 premenopausal breast cancer women who received adjuvant chemotherapy for early-stage breast cancer (Stages I-III) and found that CIA significantly related to age at diagnosis and tamoxifen usage. This result corresponded to the meta-analysis from Zavos and Valachis mentioned above [9]. In our study, 75.3% of the participants reported tamoxifen usage and this factor was not significant for permanent CIA in multivariate analysis. This different outcome might be for various reasons such as the duration of tamoxifen usage, the chemotherapy regimen, the ethnicity, and genetic backgrounds. Ruddy et al. [11] studied premenopausal breast cancer women younger than 45 years old and suggested that genetic variations with rs 147451859 on chromosome 15 and rs 17587029 on chromosome 2 were associated with resumption of menses after chemotherapy. Furthermore, Kim et al. [12] also reported 38.9% of premenopausal breast cancer women still had regular menstruation while using tamoxifen.

Concerning prognosis in patients with CIA, Zhou et al. [13] performed meta-analysis from 13 eligible studies that recruited over five thousand breast cancer

Table 4. Clinical Characteristics of Patients Still Menstruating During Chemotherapy (N=12)

SN	Age[1] (year)	Age [2] (years)	BMI (Kg/M^2)	Stage	Histology	ER	PR	HER2	Tamoxifen	Chemotherapy	Current menstrual status	Current cancer status
8	26	30	18.96	IIB	IDCA	Positive	Positive	Equivocal	Yes	ACx4 + Tx4	Still menstruating	CR
40	40	53	33.33	IIA	IDCA	Negative	Negative	Negative	No	FECx6	Still menstruating	CR
66	40	47	21.29	I	IDCA	Negative	Negative	Equivocal	No	FAC x 6	Still menstruating	CR
74	36	38	24.52	IIIA	IDCA	Negative	Negative	Positive	No	ACx4+Tx4	Still menstruating	CR
75	28	43	19.07	IIA	IDCA	Negative	Negative	Negative	No	FACx6	Menopause	Developed secondary cancer
123	33	34	30.39	IIB	IDCA	Negative	Negative	Equivocal	No	ACx4 + Tx4	Still menstruating	CR
143	47	53	20.66	IIA	IDCA	Positive	Negative	Positive	Yes	ACx4 + Tx4	Menopause	CR
164	30	45	21.78	IA	Tubula CA	Negative	Negative	Negative	No	CMF x 6	Menopause	Recurrence
172	37	40	21.97	IIIA	IDCA	Negative	Negative	Negative	No	ACx4 + Tx4	Still menstruating	CR
176	27	35	21.48	IA	IDCA	Negative	Negative	Negative	No	FAC x 6	Still menstruating	CR
186	30	33	20.2	IIB	IDCA	Positive	Positive	Equivocal	Yes	AC x 4 + TH x 4	Still menstruating	CR
188	23	24	28.55	IIA	Mucinous CA	Positive	Positive	Negative	Yes	AC x 4	Still menstruating	CR

Age[1], at received chemotherapy, Age[2], age at interview, BMI; body mass index, ER; estrogen receptor, PR; progesterone receptor, HER2; human epidermal growth factor receptor 2, IDCA; invasive ductal carcinoma, AC; Adriamycin+cyclophosphamide, T; paclitaxel, CR; complete response, FEC; fluouracil + epirubicin +cyclophosphamide, FAC; fluouracil + Adriamycin +cyclophosphamide, CMF; cyclophosphamide + methotrexate, fluorouracil, TH; trastuzumab (Herceptin), CA; carcinoma

patients to assess the exact prognostic value of CIA and reported that CIA was associated with improvement of disease-free and overall survival. However, our study did not find this benefit from irreversible CIA. The recurrence rate in patients with irreversible CIA and resumption of menstruation was not significantly different. Moreover, with 12 patients who still had normal menstruation, ten patients were still free of disease. This non-similar result might be from the limited number of our participants to compare this treatment outcome between patients with and without CIA.

The strength of our study was that all of the participants were treated in one institution. This should decrease the level of variation from the type of treatment. However, due to the nature of a retrospective study, some data was missing and more details of menstruation such as regularity before CIA and the time of resuming menstruation were not available.

In conclusion, over 90% of premenopausal women experienced CIA and one-third of them could be recover while less than 10% still had normal menstruation. The age over 45 years-old was the only independent factor related to irreversible CIA. This study did not find the association of permanent CIA and the outcome of treatment in terms of recurrence rate.

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RESEARCH ARTICLE

Risk Factors that Cause Cervical Intraepithelial Lesion Development: A Single Center Cross-sectional Study in Turkey

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Abstract

Backgrounds: Studies have been conducted in many regions to identify major and minor risk factors that play a role in the development of cervical intraepithelial lesions (CIN), which are precursors of cervical cancer. The aim of this study is to determine the major and minor risk factors for the development of CIN in a single center. **Methodology:** This study is a cross-sectional study involving 2003 patients who applied to the gynecology clinic of Adıyaman University Training and Research Hospital between January 2016 and December 2019. The relationship between cytology results and Human Papilloma Virus (HPV) presence, wart, infection presence, educational status, choice of contraceptive method, body mass index (BMI) and smoking were statistically analyzed. Binary logistic regression test was used to analyze the data. $p < 0.05$ value was considered significant. **Results:** The presence of HPV is the most important variable with 55.6% in explaining the variables on the result of colposcopy. However, HPV 16-18 positivity is 46 times, other HrHPV 5.1 times, the presence of infection in vaginal cytology 4.8 times, using combine oral contraceptive pills COC as a contraceptive method 2 times, Copper intrauterine device (Cu-IUD) use 3 times, education level 2.3 times, smoking 4.4 times and thirty and above BMI increases positivity by colposcopy 0.6 times. **Conclusions:** HPV positivity is still a major risk factor for CIN development. Contraceptive method selection, presence of vaginal infection, smoking and obesity are other risk factors that increase the risk of developing CIN.

Keywords: Copper releasing IUDs- Cervical Intraepithelial Neoplasia risk- Oral contraceptives- Human papilloma virus

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Introduction

Cervical cancer is a preventable cause of cancer with more than half a million women newly diagnosed each year [1]. It is known that cytology (Pap test) test used in cervical cancer screening decreases mortality and incidence [2]. Presence of persistent infection with Human Papilloma Virus (HPV) is associated with precancerous cervical intraepithelial neoplasia (CIN) and is a risk factor for cervical cancer [3]. Low-grade lesions are usually caused by transmission with low risk HPV types; however, persistent infections with higher risk HPV types (HRHPV) lead to high grade lesions [4]. Although persistent infection with HrHPV is an effective cause of cervical cancer; smoking, infection with other sexually transmitted diseases (Clamidya trochomatis, etc.) and hormonal contraception and hormonal imbalances are defined as cofactors that increase the development of cervical cancer when combined with high-grade cervical lesions and HPV infection for the development of cervical cancer [3]. Although there are studies showing the relationship between hormonal contraceptive methods and cervical cancer [5-6], there are conflicting publications on the use of Cooper intrauterine device (Cu-IUD) [7-8].

The aim of this study is to determine the major and minor risk factors for the development of cervical intraepithelial neoplasia in a single center.

Materials and Methods

Study Population

This study is a cross-sectional study involving patients who applied to the gynecology outpatient clinic of Adıyaman University Training and Research Hospital

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between January 2016 and December 2019. Approval was obtained for this study from the non-interventional regional ethics board committee. The study included 2003 married and monogamous patients with examination data, cervical cytology results, HPV test, colposcopy results, vaginal cytological evaluations and treatment information in the hospital database.

Exclusion criteria were the age of 18, pregnancy, a history of cervical conization, a history of previous malignancy or hematological disease, a history of chemotherapy / radiotherapy, a patient with diabetes mellitus, a history of autoimmune disease, and immunosuppressive medication.

A questionnaire was created for the patients included in the study. In the questionnaire, the patients' obstetric history (gravida, parity, abortion rates), educational status, smoking history, height and weight information, types of contraceptive methods they used and how long they used were questioned by reaching the patients. Body mass index (BMI) was calculated from height and weight data. Examination findings, vaginal cytology evaluation results, cervical cytology, colposcopic biopsy and LEEP conization results and HPV test results recorded in the database of the hospital were noted.

Statistical Analysis

SPSS 22 program was used in the analysis of the data. In the analysis of qualitative data, Chi-square test and binary logistic regression analysis were used. The group whose negative cytology result was accepted as the reference to the logistic regression model established to estimate the cytology result; HPV presence, wart, presence of infection, educational status, contraceptive method selection, BMI and cigarette use are included. The model was found compatible. Forward Stepwise method was used. Independent variables are included in the model in order. $p < 0.05$ is considered important.

Results

Sociodemographic data and clinical features of study populations

According to the use of contraceptive methods, 2003 patients who participated in the study were grouped as patients using copper IUD (Cu-IUD), those who used combined oral contraceptives (COC) and those who did not use medical contraceptives. The number of patients using Cu-IUD was 765 (38.2%), the number of patients using COC was 580 (29%) and the number of patients not using medical contraceptive method was 658 (32.9%).

The mean age of patients using Cu-IUD was measured as 39.21 ± 7.83. The mean age of patients using COC was 35.51 ± 6.64.

The levels of education, BMI, smoking, application symptoms, vaginal cytology results, presence of wart, cervical cytology results, colposcopic biopsy results, conization results and HPV positivity and positive HPV types belonging to both groups are shown in Table 1.

Table 1. Age Averages, Obstetric data, Educational Status, Symptoms, Vaginal Cytology, Cervical Cytology, Colposcopic Biopsy, Conization Results, HPV Positivity and HPV Types, BMIs and Smoking were Given

	None*	COC†	Cu-IUD‡
Age	40,29±9,79	35,51±6,64	39,21±7,83
Obstetrics			
Gravida	3,19±1,90	2,34±2,00	3,66±1,91
Parity	2,56±1,54	1,67±1,35	2,88±1,42
Abortus	0,62±0,71	0,67±0,91	0,83±1,23
Educational Status			
Middle School and Below	77 (% 11,7)	39 (% 6,8)	45 (% 5,9)
Middle School or Above	512 (% 77,8)	366 (% 63,3)	598 (% 78,2)
License	48 (% 7,3)	123 (% 19,3)	42 (% 29,9)
Master	21 (% 2,3)	50 (% 8,7)	80 (% 10,5)
Symptoms			
Discharge	315 (47,8)	260 (% 44,9)	325 (42,5)
Lower abdominal pain	70 (% 10,7)	110 (% 18,9)	140 (% 18,2)
Iching	119 (% 18,1)	70 (% 12)	160 (% 21)
Dyspareunia	14 (% 2,2)	40 (% 6,9)	60 (% 7,8)
Dysmenorrhea	140 (% 21,2)	100 (% 17,3)	80 (% 10,5)
Vaginal Cytological Diagnosis			
Normal Vaginal Flora	301 (% 47,3)	250 (% 45,4)	175 (% 24,1)
Active Inflammation	49 (% 7,7)	30 (% 5,5)	10 (% 1,4)
Candidiasis	91 (14,3)	120 (% 21,8)	160 (% 22,1)
Bacterial Vaginosis	189 (% 29,7)	120 (% 21,8)	375 (% 51,7)
Trichomonas Vaginalis	7 (% 1,1)	30 (% 5,5)	0 (% 0,0)
Chronic Cervicitis	0 (% 0,0)	0 (% 0,0)	5 (% 0,7)
Wart			
Positive	42 (% 6,4)	140 (% 24,1)	100 (% 13,1)
Negative	616 (% 93,6)	440 (% 75,9)	665 (% 86,9)
Cervical Cytology			
Negative	420 (% 63,8)	180 (% 31)	320 (% 41,8)
ASCUS§	126 (% 19,1)	160 (% 27,6)	190 (% 24,8)
LG-SIL**	70 (% 10,6)	150 (% 25,9)	150 (% 19,6)
HG-SIL (CIN II+)††	42 (%6,4)	90 (% 15,5)	105 (% 13,7)
Colposcopic Biopsy Results			
Negative	7 (% 3,8)	10 (% 2,4)	0 (% 0,0)
Chronic Cervicitis	56 (% 30,8)	20 (% 4,9)	135 (% 28,1)
LG-SIL	63 (% 34,6)	200 (% 48,8)	230 (% 47,9)
HG-SIL CINII ††	56 (% 30,8)	170 (% 41,5)	90 (% 18,8)
HG-SIL CINIII §§	0 (% 0,0)	10 (% 2,4)	25 (% 5,2)
Conization Biopsy Results			
Chronic Cervicitis	7 (7,7%)	10 (% 4,2)	25 (% 13,1)
LG-SIL	42 (% 46,2)	60 (% 25)	85 (% 44,7)
HG-SIL CINII	21 (% 23,1)	50 (% 20,8)	25 (% 13,2)
HG-SIL CINIII	21 (% 23,1)	120 (% 50)	55 (% 28,9)
HPV#			
Negative	476 (% 72,3)	140 (% 24,1)	335 (% 43,8)
Positive	182 (% 27,7)	440 (% 75,9)	430 (% 56,2)

Continued Table 1.

	None*	COC†	Cu-IUD‡
HPV Types			
HPV 16	77 (% 11,7)	160 (% 27,6)	185 (% 24,2)
HPV 18	14 (% 2,1)	40 (% 6,9)	30 (% 3,9)
OTHER HPV	91 (% 14,3)	240 (% 35,8)	215 (% 27,6)
BMI***			
<25	175 (% 26,6)	200 (% 34,5)	240 (% 31,4)
25-29,99	343 (% 52,1)	270 (% 46,6)	440 (% 57,5)
>30	140 (% 21,3)	110 (% 19)	85 (% 11,1)
Smoking			
Positive	100 (% 13,07)	80 (% 13,8)	8 (% 1,2)
Negative	665 (% 86,93)	500 (% 86,2)	650 (% 98,8)

* None, Patient group not using medical contraceptive method; †COC, Group of women using combined oral contraceptives; ‡Cu-IUD, Group of women driving intrauterine device with copper; §Atypical Squamous Cells Of Undetermined (ASCUS); **Low Grade Squamous Intraepithelial Lesion (LGSIL); ††High Grade Intraepithelial Lesion Cervical Intraepithelial Neoplasia grade II-III (HGSIL CINII-III); ‡‡High Grade Intraepithelial Lesion Cervical Intraepithelial Neoplasia grade III (HGSIL CINII); §§High Grade Intraepithelial Lesion Cervical Intraepithelial Neoplasia grade III (HGSIL CINIII); #Human Papilloma Virus; ***Body Mass Index

Analysis of CIN risk factors for groups

HPV positivity was significantly higher in women using COC (p <0.001). Wart incidence was also low in women using Cu-IUD (p <0.001). When the cervical cytology findings of women using COC and Cu-IUD were compared, it was found that the incidence of abnormal cervical cytology in both groups increased compared to the patient group who did not use medical contraceptive method (p <0.001) (Table 2).

When colposcopic biopsy results were compared, the incidence of LGSIL, HGSIL CIN II lesions was higher in patients using COC compared to the patients using Cu-IUD. In the patient group using Cu-IUD, the rate of chronic cervicitis was higher than the patient group using COC. In both patient groups using COC and using Cu-IUD; HGSIL CIN III result rates were higher than the patients who did not use medical contraceptive method (p <0.001) (Table 2).

When conization results are evaluated; While chronic cervicitis and LG-SIL rates were high in patients using Cu-IUD, HGSIL CIN II and CIN III rates were higher in those using COC(p<0.001).

Bacterial vaginosis was more common in women using Cu-IUD, while bacterial vaginosis was lower in women using COC. Trichomonas vaginalis infection was more common in women using COC (p <0.001) (Table 2).

Multivariate analysis of potential risk factors for CIN

To the logistic regression model established to estimate the result of colposcopy; HPV 16-18 Positivity, Ot HrHPV positivity, contraceptive methods and duration of use, BMI is between 25-29.99, BMI is above 30, educational status and smoking are included. Model fit was found to be good. Forward Stepwise method was used. Independent variables were included in the model in order. Those with BMI 25-29.99 and duration of contraceptive method had no significant contribution to the model.

The presence of HPV explains 55.6% of the change in colposcopy result. The effect of other variables on the change in colposcopy is 7%. HPV 16-18 presence 46 times, Ot HrHPV positivity 5.1 times, presence of infection in vaginal cytology 4.8 times, using COC as a contraceptive method 2 times and using Cu-IUD as a contraceptive method 3 times, education level 2.3 times, smoking 4.4 times and 30 BMI greater than, was found to increase the risk of colposcopy result to be positive 0.6 times (Table 3).

Discussion

This study is a cross-sectional study of data analysis retrospectively, but supported by one-to-one surveys. In addition, while determining the epidemiological factors of patients, a questionnaire was conducted to prevent bias.

The selection of contraceptive methods and the effect of the selected contraceptive methods on the development of CIN and potential risk factors that may affect the development of CIN were investigated in patients who applied to our center. This study, conducted in a large population of Turkish women, is a featured study comparing the effect of contraceptive methods on CIN development and other risk factors causing cervical cancer development.

It is a major factor in HPV CIN development and invasive cervical cancer development [9]. It has been reported that HPV 16 and 18 types cause CIN III development more frequently than HPV 16 than Ot HrHPV types [10]. In our study, HPV positivity, especially HPV 16-18 positivity, has been shown to increase the risk of CIN compared to Ot Hr HPV types.

In a recent metaanalysis, it has been reported that the use of Cu-IUD increases HPV clearance and prevents persistent infection [11]. In our study, HPV positivity was more common in patients using COC.

In a recent study by Loopik et al (2020); reported that there was an increased risk of developing CIN III lesions compared to non-users with both COC use and Cu-IUD use. They also reported that this risk is higher in women using COC compared to women using Cu-IUD [12]. These findings support our study. As a result of colposcopic biopsy in our study, it was found that the frequency of LG-SIL and HG-SIL CIN II lesions were more common in those using COC. In contrast, in the patient group using both COC and Cu-IUD, the rate of HG-SIL CIN III lesion detection was higher than the group not using a medical contraceptive method. In addition, while the frequency of incidence of HGSIL CIN II and CIN III lesions was higher in the patient group using COC in patients with conization compared to those using Cu-IUD; LG-SIL rates were higher in the patient group using Cu-IUD.

In a cross-sectional study examining patients in the California health system; No increase in frequency of HG-SIL CIN II and CIN III lesions was reported in those using Cu-IUD; however, there was an increase in the frequency of HG-SIL CIN II lesions in users of levonorgesterone Intrauterine Device (LNG-IUD). In our

Table 2. HPV Positivity, Presence of Wart, Cervical Cytology, Colposcopic Biopsy, Conization Results, and Frequency of Vaginal Cytology Results were Shown in Women Using Cu-IUD, Women Using COC, and Women not Using Medical Contraceptives.

	None	COC	Cu-IUD	
HPV#				
Positive	182	440	430	
	(% 27,7)	(% 75,9)	(% 56,2)	P<0,001
Negative	476	140	335	
	(% 72,3)	(% 24,1)	(% 43,8)	
Wart				
Negative	616	440	665	
	93,6 %	75,9 %	86,9 %	P<0,001
Positive	42	140	100	
	6,4 %	24,1 %	13,1 %	
Cervical Cytology				
Negative	420	180	320	
	63,8	31,0	41,8	
ASCUS†	126	160	190	
	19,1	27,6	24,8	<0,001
LG-SIL‡	70	150	150	
	10,6	25,9	19,6	
HG-SIL (CINII+)§	42	90	105	
	6,4	15,5	13,7	
Colposcopy Results				
Negative	7	10	0	
	3,8 %	2,4 %	0,0 %	
Chronic Cervicitis	56	20	135	
	30,8 %	4,9 %	28,1 %	
LG-SIL	63	200	230	<0,001
	34,6 %	48,8 %	47,9 %	
HG-SIL CINII**	56	170	90	
	30,8 %	41,5 %	18,8 %	
HG-SIL CINIII*	0	10	25	
	0,0 %	2,4 %	5,2 %	
Conization Results				
Chronic Cervicitis	7	10	25	
	7,7 %	4,2 %	13,1 %	
LG-SIL	42	60	85	
	46,2 %	25,0 %	44,7 %	
HG-SIL CINII	21a	50a	25a	
	23,1 %	20,8 %	13,2 %	P<0,001
HG-SIL CINIII	21	120	55	
	23,1 %	50 %	28,9 %	
Vaginal Cytology				
Normal vaginal flora	301	250	175	
	(% 47,3)	(% 45,4)	(% 24,1)	
Active Inflamation	49	30	10	
	(% 7,7)	(% 5,5)	(% 1,4)	
Candidiyasis	91	120	160	
	(14,3)	(% 21,8)	(% 22,1)	
Bacterial Vaginosis	189	120	375	
	(% 29,7)	(% 21,8)	(% 51,7)	

Continued Table 2.

	None	COC	Cu-IUD	
Vaginal Cytology				
Trichomonas Vaginalis	7	30	0	
	(% 1,1)	(% 5,5)	(% 0,0)	

#HPV, Human Papilloma Virus; †ASCUS, Atypical Squamous Cells of Undetermined; ‡LGSIL, Low Grade Squamous İntraepithelial Lesion; §HGSIL CINII+, High Grade İntraepithelial Lesion Cervical İntraepithelial Neoplasia grade II-III;**HGSIL CINII, High Grade İntraepithelial Lesion Cervical İntraepithelial Neoplasia grade II; *HGSIL CIN III, High Grade İntraepithelial Lesion Cervical İntraepithelial Neoplasia grade III

study, there was no patient group using LNG-IUD, but contrary to this study, the rate of HG SIL CIN III lesion detection increased in patients using Cu-IUD compared to the group that did not use a medical contraceptive method. In contrast, in our study, the risk of developing CIN in women using Cu-IUD has been shown to be higher than women who use COC. It may be wrong to link it only to HPV positivity. According to the author; multifactorial evaluation is effective in this result.

Previous studies have shown that the use of Cu-IUD causes acute / chronic vaginal and cervical infections, and it has been shown that the vaginal flora changes with the use of Cu-IUD. Moreover, the frequency of bacterial vaginosis in these studies increased in women using Cu-IUD [13-15]. In our study, similar to these studies, there is an increase in the frequency of BV and other infectious agents except trichomonas vaginalis in patients using Cu-IUD. Also, in our study, the frequency of chronic cervicitis increased in both colposcopic biopsy results and conization results in the patient group using Cu-IUD.

In a recent study, the relationship between the presence of vaginal infection and CIN lesions has been investigated, and in these studies, it has been stated that the presence of vaginal infection may be a risk factor for cervical cancer by reducing HPV clearance [16]. In our study, the presence of vaginal infection in regression testing has been shown to play a role in the development of CIN. Given this effect of infection development on CIN, the increased risk for CIN in the patient group using Cu-IUD is not a surprise.

It has been reported that smoking is a cofactor that increases the development of CIN in patients using COC [3]. According to the results in our study, smoking increased the risk of developing CIN.

It has been stated that preventing obesity by creating BMI screening programs may decrease the development of cervical cancer [17]. It can be seen in this study that obesity has a minimal contribution to the development of CIN.

In our study, it was found that the level of education also contributed to the development of CIN. According to the author, this may also be related to the socioeconomic cultures of patients. Larger patient groups are needed to investigate this finding.

This study has some limitations. First, this study is a cross-sectional study conducted by examining retrospective data. Therefore, there may be bias in the data. However, this deficiency was tried to be eliminated with the questionnaires. Another limitation is that the

Table 3. Binary Logistic Regression Test Results for Determining Risk Factors for Cervical Intraepithelial Lesion Development

	B*	p	OR†	95% C.I. ‡ for OR	
				Lower	Upper
HPV§					
HPV 16-18 Positive	3,835	<0,001	46,271	33,517	63,878
Other HrHPV**	1,642	<0,001	5,166	3,201	8,338
Education Status	0,853	<0,001	2,346	1,558	3,533
Vaginal Infection	1,577	<0,001	4,841	2,796	8,383
Contraceptive Methods		<0,001			
COCs††	0,702	<0,001	2,017	1,432	2,841
Cu-IUDs‡‡	1,101	<0,001	3,007	2,185	4,140
BMI §§		0,004			
BMI(25-29,9)	0,193	0,226	1,213	0,887	1,658
BMI(>30)	-0,436	0,037	0,647	0,429	0,975
Smoking	1,494	<0,001	4,455	2,399	8,275
Constant	-1,045	<0,001	,352		

*β, coefficient; †O.R., Odds Ratio; ‡C.I., Confidence Interval; § HPV, Human Papilloma Virus;**Other High Risk HPV; †† COC, Group of women using combined oral contraceptives; ‡‡Cu-IUD, Group of women driving intrauterine device with copper; §§ BMI, Body Mass Index.

study was conducted in a single center. Studies on heterogeneous groups may be required. These limitations need to be considered before generalizing the data.

In conclusion; HPV positivity is still a major risk factor for CIN development. Contraceptive method selection, presence of vaginal infection, smoking and obesity are other risk factors that increase the risk of developing CIN.

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Conflict of interest

The authors declare no conflict of interest.

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RESEARCH ARTICLE

Incidence and Associated Risk Factors of Patients with Malignant Transformation Arising in Mature Cystic Teratoma of the Ovary in Rajavithi Hospital

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Abstract

Objectives: To review the incidence and evaluate risk factors associated with malignant transformation in mature cystic teratoma (MCT) of the ovary. **Methods:** A retrospective medical record review for 571 patients diagnosed as ovarian MCT who were treated at Rajavithi Hospital from January 2005 to June 2017 was performed. The demographics data, preoperative investigations, pathological findings, adjuvant treatments, and follow-up outcomes were obtained and analyzed. **Results:** Forty patients with malignant transformation in MCT were detected over a period of 12 years. The incidence rate was 7% of all MCT. Squamous cell carcinoma was the most common histologic type (45%) and the most of them were stage I (80%). Patients with malignant transformation were significantly older than those benign MCT (48.4 years vs 37.5 years, p<0.001). The mean largest diameter of the tumor in the malignant group was significantly larger than the benign group (15.5 cm. vs 8.3 cm., p<0.001). The mean serum CA-125 levels in the malignant group was 83.2 U/mL and higher than 30.3 U/mL in benign group (p<0.001). In multivariate analysis, largest tumor diameter >10 cm. (OR 6.68; 95%CI, 2.39-18.65), solid part from ultrasound findings (OR 5.30; 95%CI, 1.63-17.24), and RMI score ≥200 (OR 8.69; 95%CI, 1.68-44.89) were a significant predictor of malignant transformation arising in MCT. Performance validation with a cut-off level of RMI ≥200 showed the AUC was 0.879, with 47.5% sensitivity, 98.4% specificity, 82.6 % positive predictive value, and 92.2% negative predictive value, respectively. **Conclusion:** Early detection and complete surgical resection of ovarian cancer are important for a long-term survival. Large tumor size and solid part from ultrasound finding were associated with malignant transformation in MCT. Additionally, calculating RMI score might be a useful diagnostic tool to detect malignancy in this setting, and adequate staging surgery should also be considered.

Keywords: Mature cystic teratoma- ovary- malignant transformation- incidence- RMI score

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Introduction

Mature cystic teratoma (MCT) or dermoid cyst of the ovary is the most common type of ovarian teratoma and germ cell neoplasm which comprising of 10-20% of ovarian tumors [1]. It is one of the most common ovarian tumors in both adolescents and women of reproductive age [2]. MCT comprises of mature tissues of ectodermal (skin, brain), mesodermal (muscle, fat), and endodermal (mucinous) layers [3-4]. Most patients with MCT are asymptomatic but can develop pain due to torsion, rupture or infection and a sensation of abdominal fullness due to mass effect [4-5].

MCT is usually benign, however, it may undergo the malignant transformation with a rate of 0.8-2.4% [6-8]. More than 80% of malignant transformations are squamous cell carcinomas arising from ectoderm, followed by adenocarcinomas. The others include malignant melanoma, sarcoma, basal cell carcinoma, carcinoid tumor, and thyroid carcinoma [8-10]. Compared

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to the benign MCT, malignant transformation occurs in an older population, with a mean age range of 45-60 years and generally postmenopausal status [11]. Moreover, patients with malignant transformation of MCT are typically present with a rapidly enlarging tumor or systemic symptoms suggestive of malignancy. The prognosis of these malignancies has been reported to be poor especially disease has spread beyond the ovary [12].

MCT is common and benign, so surgery may frequently be postponed after a clinical diagnosis of MCT, especially in young women with reproductive age. In some case that misdiagnosed preoperatively, complete surgical resection is not performed, consequently harming the prognosis of the patients. Thus, early detection of malignant transformation of MCT is important when treating patients before metastasis occurs.

However, preoperative or even intraoperative diagnosis of malignant transformation of MCT is very difficult and rarely diagnosed due to the rarity of this tumor and its similarly to MCT. An elevated pre-operative serum level of SCC antigen may be a useful marker to detect malignant transformation in MCT, but the serum SCC antigen level depends on the tumor volume, so it may not be suitable for small tumors [13-14].

In this study, we analyzed our experience with these rare tumors in a retrospective analysis. The primary objective was to review the incidence of malignant transformation in MCT of the ovary at Rajavithi Hospital. The secondary objective was to evaluate the risk factors associated with malignant transformation in MCT of the ovary in order to identify the patients who suspected malignancy before the time of surgery.

Materials and Methods

After receiving approval from the Institutional Review Board of the Rajavithi Hospital, medical records, pathologic reports, and follow up outcomes were reviewed retrospectively for all patients treated for MCT between January 2005 and June 2017 at Rajavithi Hospital. Patients were excluded if they had a history of other or synchronous cancers, received neoadjuvant chemotherapy, or incomplete medical record such as pathological reports. Clinical variables extracted from the records include patient's baseline characteristics, preoperative investigations, operative procedures, pathologic findings, and type of adjuvant therapy. Based on the data obtained, RMI score were also calculated for patients who had the data included serum CA-125 levels to indicate malignancy [15]. In patients who had undergone surgery in other hospital and referred to our institute, pathologic slides were reviewed by a pathologist at Rajavithi Hospital. Surgical staging was classified by using International Federation of Gynecology and Obstetrics (FIGO) 2014 system [16]. The follow-up outcomes include recurrence and survival data were reviewed.

Patients were assigned to two groups (benign and malignant MCT patients) based on the pathological diagnosis. Statistical analysis of various clinicopathologic characteristics was performed with SPSS version 16.0. Student's t-test and the Mann-Whitney U-statistic were used for continuous variables, and the chi-square test or Fisher's exact test was used for categorical variables. Univariate and multiple logistic regression was performed to evaluate for unadjusted and adjusted associations between prognostic factors and malignant transformation in MCT. The results were expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs), calculated by the Wald method.

Receiver operator characteristics (ROC) curves were constructed and the areas under the curve (AUC) with binomial exact 95% confidence intervals (95% CI) were calculated. The diagnostic performance of the models was also expressed as sensitivity, specificity, positive and negative predictive values when using the recommended cut-off values for each predictive variable.

Survival analysis of malignant MCT patients was also evaluated using the Kaplan-Meier method. The endpoints of the analysis were recurrence-free survival (RFS) and overall survival (OS). RFS was defined as the time interval from pathological diagnosis date to the first evidence of recurrence or death from any cause. OS was defined as the time between diagnosis and death. Patients alive at their last follow up visit were censored. All statistical tests were 2-sided, and differences were considered statistically significant at a probability value of < 0.05.

Results

According to our medical records, 571 patients with ovarian MCT received treatment at Rajavithi Hospital during the study periods. After review of pathological reports of these patients, 40 patients with malignant transformation in MCT were identified. Therefore, the incidence rate of malignant transformation in MCT

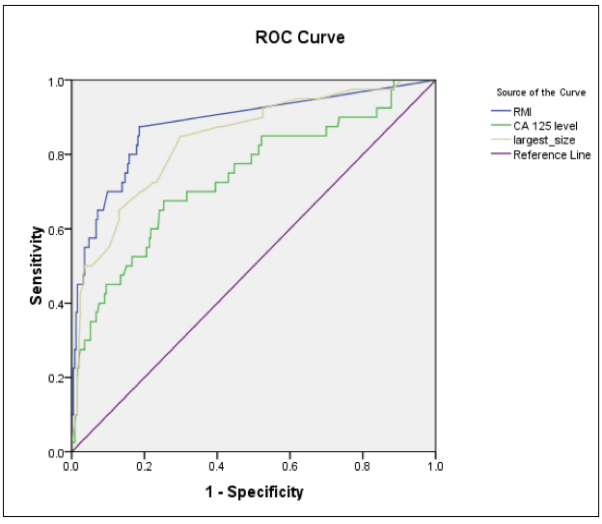

Figure 1. Receiver Operating Characerisics (ROC) Curve Showing the Relattionships between Sensitivity and Specificity of Predicive Factors in Discrimination between Mature Cystic Teratoma and Malignancy Arisinng in Mature Cystic Teratoma of Ovary

Table 1. Baseline Characteristics of Benign and Malignant Mature Cystic Teratoma of the Ovary

Variables	Malignancy (N=40)		Benign (N=419)		p-value
Age (mean, years ± SD)	48.4 ± 14.2		37.5 ± 14.8		< 0.001*
Nationality					0.152
Thai	40	100%	393	93.80%	
Others	0	0%	26	6.20%	
BMI (kg/m^2)					0.722
< 25	27	67.50%	293	69.90%	
≥ 25	13	32.50%	126	30.10%	
Para					0.098
Nulliparous	14	35%	207	49.40%	
Multiparous	26	65%	212	50.60%	
Menopause					0.002*
Pre-menopause	23	57.50%	339	80.90%	
Post-menopause	17	42.50%	80	19.10%	
Presenting symptoms					0.008*
Pelvic mass	30	75%	301	71.80%	
Pelvic pain	5	12.50%	43	10.30%	
Abdominal discomfort	3	7.50%	15	3.60%	
Pregnancy	0	0%	45	10.70%	
Others	2	5.30%	15	3.60%	
Ultrasound findings					< 0.001*
Cystic	5	12.50%	360	85.90%	
Multi-septate	14	35%	14	3.30%	
Solid part	21	52.50%	20	4.80%	
Calcification	0	0%	9	2.10%	
Others	0	0%	16	3.80%	
Serum CA 125 level (mean, U/mL ± SD)	83.22 ± 103.56		30.28 ± 38.27		< 0.001*
< 35	16	40%	195	77.10%	
≥ 35	24	60%	58	22.90%	
Tumor size (mean, cm. ± SD)	15.5 ± 6.0		8.3 ± 3.8		< 0.001*
RMI score (mean, ± SD)	254.13 ± 302.72		17.46 ± 61.92		< 0.001*
< 200	21	52.50%	249	98.40%	
≥ 200	19	47.50%	4	1.60%	
Type of surgery					< 0.001*
Conservative surgery	7	17.50%	336	80.20%	
Radical surgery	33	82.50%	83	19.80%	

Abbreviations, BMI; body mass index

was 7%.

Of these 571 patients, 112 patients were excluded because they no longer fulfilled the inclusion criteria, incomplete medical records, and were lost at follow up. Therefore, a total of 459 patients were successfully analyzed for our study and they were classified into two groups; 419 patients with benign ovarian MCT and 40 patients with malignant transformation in MCT.

Table 1 showed the baseline characteristics of benign and malignant MCT patients. Patients with malignant transformation were significantly older than those with benign MCT (48.4 years vs 37.5 years, p<0.001) and the most case were pre-menopause (p=0.002). The most common presenting symptom was pelvic mass (p=0.008) and few cases were incidental findings. All patients underwent ultrasonography and we found that almost all ultrasound finding of benign group was cystic (85.9%). In contrast, the most ultrasound finding of malignant group was solid part (52.5%). The mean diameter of the largest tumor before surgery was 15.5 cm. in the malignant group, which was significantly larger compared to the benign group (p<0.001).

To evaluate the tumor markers, serum CA-125 levels were measured in 293 patients before surgery. The mean serum CA-125 level was 83.2 U/mL in the malignant group, which was significantly higher than the benign

Table 2. Characteristic of Malignancy Arising in Mature Cystic Teratoma of the Ovary

Variables	N (Total = 40)	Percent (%)
Histopathology		
Squamous cell carcinoma	18	45
Adenocarcinoma	10	25
Others	12	30
Grade		
1	25	62.5
2	8	20
3	7	17.5
Type of surgery		
USO/BSO	12	30
Hysterectomy with BSO	8	20
Complete surgical staging	18	45
Others	2	5
Optimal surgery	37	92.5
Staging		
Early stage	38	95
Advanced stage	2	5
Pathologic findings		
Intraoperative rupture	11	27.5
Capsule involvement	11	27.5
LVSI positive	2	5
Presence ascites	6	15
Omental metastasis	4	10
Receive adjuvant treatments	24	60
Chemotherapeutic regimens		
Single agent chemotherapy	2	5
Combined agent chemotherapy	22	55
Response		
CR	38	95
PR	1	2.5
PD	1	2.5
Recurrence of disease	7	17.5
Site of recurrence		
Local recurrence	5	71.4
Distant recurrence	2	28.6
Treatment of recurrence		
Surgery	1	14.3
Chemotherapy	6	85.7
Death	10	25
Cause of deaths		
Cancer	7	17.5
Non-cancer	3	7.5

Abbreviations, USO/BSO; unilateral/bilateral salpingo-oophorectomy, LVSI; lymphovascular invasion, CR; complete response, PR; partial response, PD; progression of disease

group ($p<0.001$). RMI Score were higher than a cut off levels of 200 in 19 patients (47.5%) with malignancy and in 4 patients (1.6%) with benign MCT ($p<0.001$). Interestingly, the results of RMI score were within the low levels in almost all patients with benign MCT and a half of patients with malignant MCT.

Characteristic of patients with malignant transformation arising in MCT are summarized in Table 2. Squamous cell carcinoma was the most common histologic type (45%) followed by mucinous carcinoma (22.5%), and endometrioid carcinoma (2.5%). The other pathologic results were carcinoid tumor, papillary serous carcinoma, malignant melanoma, papillary thyroid carcinoma, follicular thyroid carcinoma, adenosquamous carcinoma, and unclassified adenocarcinoma. Most cases (62.5%) presented with well differentiated tumor.

A half of patients (45%) underwent complete surgical staging and the most of them (80%) were obtained optimal surgical resection. Thirty-two patients (80%) were stage I, while stage II was found in 6 patients (15%). One patient was stage III and another one was stage IV. Adjuvant treatment with combined chemotherapy was offered in more than half of all patients and the follow-up outcomes showed a good prognosis in RFS and OS. The chemotherapeutic regimens were single cisplatin for one patient, single carboplatin for one patient, a combination of paclitaxel and platinum for eight patients, a combination of cisplatin and 5-fluorouracil for four patients, a combination of cyclophosphamide and platinum for four patients, a combination of etoposide and cisplatin for one patient, a combination of bleomycin, etoposide, and cisplatin for three patients, and a combination of vincristine, actinomycin, and cyclophosphamide for one patient.

Table 3 showed univariate analysis and multivariate analysis for predictive factors of malignancy arising in MCT. Univariate analysis for predictive factors of malignant transformation arising in MCT revealed that age older than 40 years (OR 5.99; 95%CI, 2.78-12.91), premenopausal status (OR 3.13; 95%CI, 1.60-6.14), tumor diameters greater than 10 cm (OR 9.00; 95%CI, 4.29-18.86), solid parts form ultrasound finding (OR 6.55; 95%CI, 3.26-13.19), serum CA 125 greater or equal than 35 U/mL (OR 5.04; 95%CI, 2.51-10.13), and a high RMI score greater than 200 (OR 56.32; 95%CI, 17.54-180.85) were significant prognostic factors. Finally, we found that tumor diameters greater than 10 cm. (OR 6.68; 95%CI, 2.39-18.65), solid parts from ultrasound findings (OR 5.30; 95%CI, 1.63-17.24), and RMI score greater than 200 (OR 8.69; 95%CI, 1.68-44.89) were significant predictive factors of malignant transformation arising in MCT in multivariate analysis.

RMI score was the predictive factor with the highest sensitivity and specificity, and largest tumor size was the second best. ROC curves were drawn to evaluate useful factors for screening and to determine the optimal cutoff values (Figure 1). The area under the curve (AUC) for each factor was as follows: RMI score, 0.879; largest tumor size, 0.840; and CA 125, 0.739; and. This suggested that RMI score were superior to the other predictive factors for screening. Performance validation with a cut-off level of RMI > 200 showed the AUC was 0.879, with 47.5% sensitivity, 98.4% specificity, 82.6 % positive predictive value, and 92.2% negative predictive value.

Based on the ROC analysis, the sensitivity, the

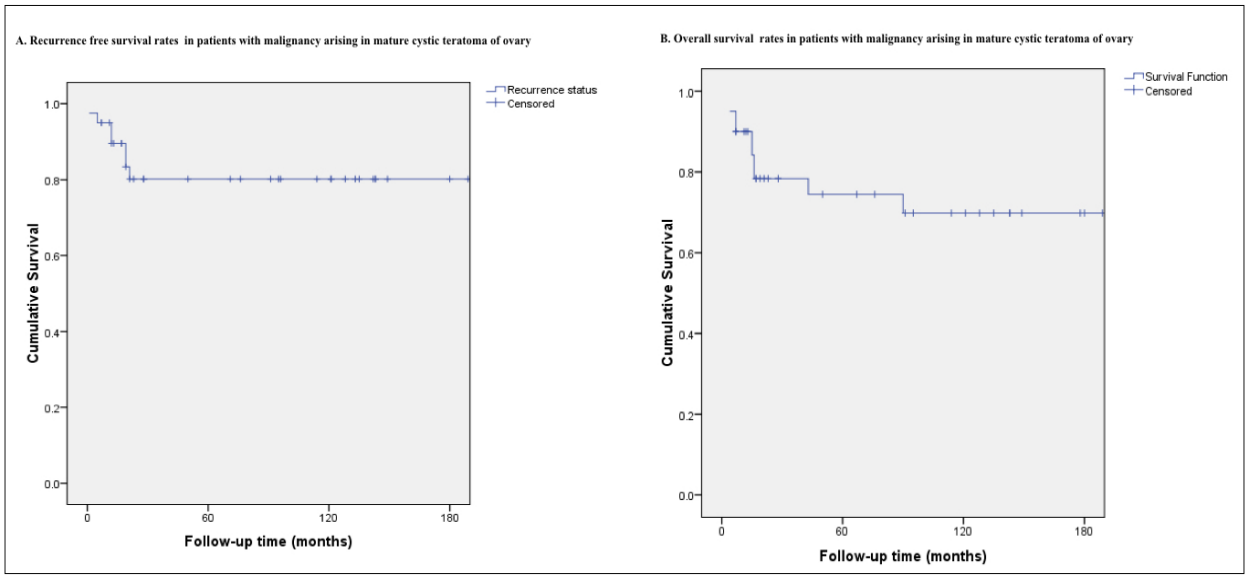

Figure 2. Survival Analysis of Patients with Malignancy Arising in Mature Cystic Teratoma of Ovary; A. Recurrence free Survival, B. Overall Survival

specificity, and the diagnostic efficiency were recalculated using the optimal cutoff values, which showed a higher diagnostic efficiency than the standard cutoff values (Figure 1 and Table 4). The best cut-off of RMI score from ROC curve was 12 with 80% sensitivity and 82.2% specificity.

The mean and median follow-up times were 78.6 and 35.5 months, respectively. One patient (2.5%) had progressive disease after surgery and seven patients (17.5%) had recurrence. The median time interval from the diagnosis to recurrence was 12 months (range, 1-21 months). The most site of recurrent disease were pelvic recurrence (71.4%). The 5-years recurrence free survival rate was 80.2% (Figure 2A). Ten patients (25%) died of the disease during follow-up. The median time to dead was 15 months (range, 4-90 months). The overall 5-years survival rate was 74.5% (Figure 2B).

Discussion

Malignant transformation arising in MCT is one of the most serious complications of MCT. Although only 0.8% to 2.4% of MCT undergo malignant transformation, the prognosis is very poor [6-8-17]. The preoperative diagnosis of malignant transformation in MCT is very difficult, and the definitive diagnosis should be provided postoperatively. By making this diagnosis prior to surgery, the most appropriate surgery can be planned and earlier consideration may be given to chemotherapy in this aggressive disease.

According to our retrospective study, we found that the incident rate of malignant transformation in our institution was 7% (40/571) which was higher than the previous reports. The explanation can be attributed to our institution being a tertiary care center where is the patients with an advanced disease or suspected malignancy are being referred from a peripheral center.

Patients with malignant transformation arising in MCT are typically postmenopausal status and may present with a rapidly enlarging tumor or symptoms suggestive of malignancy. Most of our patients also presented with palpable pelvic mass and there was consistent with previous studies [9-17]. Several literatures found that advanced age increased the risk of malignant arising in MCT whereas the present study was not showed [7-13-18]. A higher percentage (78.9%) of premenopausal women

Table 3. Predictive Factors for Malignancy Arising in Mature Cystic Teratoma of the Ovary

Variables	Univariate analysis		Multivariate analysis	
	OR	95%CI	OR	95%CI
Age (≤ 40 years vs > 40 years)	5.99*	2.78 – 12.91	3.36	0.92 – 12.23
Menopausal status (pre- vs post-)	3.13*	1.60 – 6.14	0.29	0.08 – 1.027
BMI (< 25 kg/m^2 vs ≥ 25 kg/m^2)	1.12	0.56 – 2.24	-	-
Present of pelvic mass (yes vs no)	0.85	0.40 – 1.79	-	-
Largest tumor diameter (≤ 10 cm. vs > 10 cm.)	9.00*	4.29 – 18.86	6.68*	2.39 – 18.65
Ultrasound findings (non-solid vs solid)	6.55*	3.26 – 13.19	5.30*	1.63 – 17.24
Serum CA125 levels (< 35 U/mL vs ≥ 35 U/mL)	5.04*	2.51 – 10.13	2.14	0.68 – 6.79
RMI score (< 200 vs ≥ 200)	56.32*	17.54 – 180.85	8.69*	1.68 – 44.89

Abbreviations, BMI; body mass index

Table 4. Diagnostic Performance of RMI, Tumor Size, and Serum CA 125 Levels in Discrimination between Mature Cystic Teratoma and Malignancy Arising in Mature Cystic Teratoma of Ovary

Variables	Cut-off levels	Sensitivity (%)	Specificity(%)	PPV (%)	NPV (%)	AUC (95%CI)
RMI	12	80	82.2	41.6	96.3	0.879 (0.813 - 0.945)
RMI	200	47.5	98.4	82.6	92.2	0.879 (0.813-0.945)
Tumor size	10 cm.	72.5	77.6	23.6	96.7	0.840 (0.770-0.909)
CA 125 levels	35 U/mL	60	77.1	29.3	92.4	0.739 (0.648-0.830)

may be the explanation. Kikkawa et al. [13] and Yamanaka et al. [18] reported that a tumor diameter of greater than 9.9 cm was 86% sensitivity for malignancy in their series, and our study reported similar results. The mean tumor size of patients with malignant transform MCT in our study was 15.5 cm. compared to 8.3 cm. in benign MCT. Moreover, ROC analysis resulted in a high AUC of 0.840 which suggested that tumor size was useful in the differential diagnosis of malignant and benign MCT.

Kido et al. [19] suggested that some imaging characteristics may be helpful in the preoperative diagnosis of malignant transformation arising in MCT such as an area of the solid component with contrast enhancement, transmural extension, and irregular invasion to the peritoneal cavity. In our study, all patients had abdominopelvic ultrasonography and a multivariate analysis showed patients who had solid portions have a 5-fold risk of malignant MCT.

The usefulness of tumor markers in malignant transformation arising in MCT is not clearly understood. High concentrations of tumor markers such as SCC Ag level and CA 19-9 have been reported in patients with malignant MCT [20-22]. In our series, we could not assess these variables because of lack of data, recommendation for future clinical research to evaluate a useful tumor marker in a distinction between malignant and benign MCT include SCC Ag level, CA 19-9 levels, and CEA with a prospective design.

From the current study, the results of RMI score were within the low levels in almost all patients with benign MCT and a half of patients with malignant MCT. A low level of RMI score due to a higher percentage of stage I ovarian cancer that always no rising in CA 125 levels [23]. Another reason may be ultrasound findings showed only solid parts that also made the low level of ultrasound score. However, ROC analysis of RMI score resulted in a high AUC of 0.879 with the best cut-off of 12. Performance validation showed the sensitivity of 80% and specificity of 82.2%. These finding suggested that a high level of RMI score of greater than 12 in patients with MCT may be suspected of malignancy and guided as a tool to select these patients for referral to a gynecologic oncologist.

Due to the rarity of malignant transformation arising in MCT, there is a lack of data on the optimal treatment option. Multimodality therapy including optimal cytoreductive surgery followed by chemotherapy and/or radiation therapy has been recommended [9-17-24-25]. However, the appropriate adjuvant therapy for these patients has not been established. There were several previous studies supporting platinum-based chemotherapy as an effective drug for advanced ovarian cancer and SCC of the cervix [8-21-24-25]. The most of our patients were obtained optimal cytoreductive surgery and 80% of them were in stage I. All of our patients whose stage beyond IB were received adjuvant chemotherapy and the most common regimen was a combination platinum-based chemotherapy such as paclitaxel and carboplatin, paclitaxel and cisplatin, and a combination of bleomycin, etoposide, and cisplatin. Similarly, we found that most patients who receive optimal cytoreductive surgery and adjuvant treatment had an extended progression-free interval and excellent prognosis with the overall 5-year survival rate of 74.5%.

A limitation of the present study is the retrospective study design, it could be prone to a recall bias and lack of some important data such as tumor markers especially in benign MCT group. In our study, we found that serum CA 125 levels were assessed in only 253 patients with benign MCT and it may be a reason for not showing a performance validation in distinguishing between malignant benign MCT. Another limitation is a single institutional study was made, it could be limited sampling population and no validation in other population.

In conclusion, these findings demonstrate that incidence of malignancy arising in MCT was 7%. For associated risk factors, large tumor size and solid part from ultrasound finding are important factors in making a differential diagnosis of malignancy arising in MCT and MCT. Additionally, calculating RMI score might be a useful diagnostic tool to detect malignancy in this setting, and adequate staging surgery should also be considered.

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Conflict of interest

The authors declared no conflict of interest.

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SHORT COMMUNICATION

Five-year Survival Predictors for Breast Cancer in Women: A Retrospective Cohort Study

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Abstract

Objective: To analyze predictors of 5-year survival in women with breast cancer in the state of Sergipe. **Materials and methods:** This is a retrospective cohort study. This study included 100 women aged between 21 and 77 years diagnosed with breast cancer undergoing adjuvant or neoadjuvant chemotherapy in a public tertiary hospital from August 2011 to December 2012. All women were followed up for 5 years or until the date of death. There was no loss in follow-up. Data were collected during the field visit to the specialized health unit and included demographic and socioeconomic variables, tumor staging at diagnosis, patient paths for presentation to health professionals, initial treatment in primary care and treatment. We used a three-stage model: the first ("patient delay"); the second ("delay in diagnosis") and the third ("delay in treatment"). The statistical analysis was performed using the MedCalc version 18 statistical software. The study was approved by the Human Research Ethics Committee of the Federal University of Sergipe (CAAE: 0196.0.107.000-11). Written informed consent was obtained from all participants. **Results:** Tumor staging [risk ratio (HR) = 3.41, p = 0.046] was an independent factor that affected the overall survival curve for women with breast cancer. The overall 5-year survival rates found for women with tumor staging IA-IIB compared to tumor staging IIIA-IV were 88.5% and 59.5%, respectively. Through binary logistic regression with forced entry method, it was evident that age (OR = 2.58, p = 0.050), delay in the first stage (OR = 2.57, p = 0.046) and tumor staging (OR = 3.99, p = 0.042) were predictors of mortality in women with breast cancer. **Conclusions:** Our results highlight the need to strengthen health education actions in primary health care and the implementation of an organized and permanent screening program for the early detection of breast cancer.

Keywords: Breast neoplasm- prognosis- survival analysis- primary health care- delayed diagnosis

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Introduction

Breast cancer is the most common non-cutaneous malignancy worldwide and the leading cause of cancer death in women. In Brazil, it is estimated nearly 60,000 new cases of breast cancer and 14 deaths per 100,000 women in 2018 [1]. A recent study showed an increased trend of breast cancer mortality in women in Brazil, especially among young women and in the Northeast and Midwest regions [2].

Differences in survival from breast cancer observed seem to be related to socioeconomic inequities and disparities in access to health services which may lead in delay in diagnosis and treatment of disease [3-4].The delay in attention to breast cancer greater than three months between the identification of symptoms and initiation of treatment is considered an important prognostic factor, decreasing by 12% the survival in five years [5].

In addition actions of screening, diagnosis and treatment should be available to the population independently of their income [6], because the staging profile of women with breast cancer has been characterized by advanced stages of the disease, evidencing the late diagnosis as a national public health issue [7]. We investigated

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predictors of 5-year survival in women with breast cancer in Sergipe state.

Materials and Methods

Design

Little is known about the influence of survival predictors for breast cancer in the Northeast region, Brazil. In this retrospective cohort study, we investigate predictors of 5-year survival in women with breast cancer in Sergipe state, the smallest federal unit in terms of territory extension (21,918 km^2). Sergipe has one of the most incidence rates of breast cancer in Brazil, with 6.34 new cases per 100.000 women [1].

Pacients

This study included 100 women aged 21-77 years (51 ± 10.9 years) diagnosed as having breast cancer submitted to adjuvant or neoadjuvant chemotherapy in a tertiary-level public hospital from August 2011 to December 2012. All women were followed-up for 5 years or to date of death. There was no loss to follow-up. Data were collected during field visit in the specialized health care unit and included demographic and socioeconomic variables, tumor staging at diagnosis [8], patient pathways to presentation to health care professionals, initial management in primary care, and treatment. We used a three-stage model [9] to account for the total time from first noticing a symptom to beginning treatment. The first stage ("patient delay")was defined as the time the patient first noticing a symptom until to seek professional medical care; the second stage ("diagnosis delay") described the time between the first medical consultation and definitive diagnosis of breast cancer; and the third stage ("treatment delay") included the time between diagnosis and the onset of treatment.

Analyses statistics

Statistical analysis was performed using MedCalc Statistical Software version 18 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Survival curves were presented as Kaplan-Meier curves, and significance was classified by the log-rank test. The Cox regression model was used for multivariate prognostic analysis, and a binary logistic regression model was used to analyze the influencing clinical factors. Analyses were performed using cutoffs of 30 (patient and diagnosis delay) and 60 (treatment delay) days [10-11]. Eight potential predictors (age, relationship status, years of schooling, income, residence, tumor staging, delay in first, second and third stages) were included in a multifactor analysis using the Cox multivariate regression model with a forced entry method.

Ethical approval

The study was approved by the Human Research Ethics Committee at the Federal University of Sergipe (CAAE: 0196.0.107.000-11). Informed written consent was obtained from all participants.

Results and Discussion

The results showed that tumor staging [hazard ratio (HR) = 3.41, p = 0.046] was an independent factor affecting the overall survival curve of women with breast cancer (Table 1). The 5-year overall survival rates found for women with tumor staging IA-IIB compared to tumor staging IIIA-IV were 88.5% and 59.5%, respectively (Figure 1). The same eight potential predictors were also analyzed by using a binary logistic regression model with a forced entry method. The results showed that age (OR=2.58, p =0.050), delay in first stage (OR=2.57, p =0.046), and tumor staging (OR=3.99, p = 0.042) were predictors for mortality in women with breast cancer (Table 2).

The advanced stage of breast cancer found in this study seems to be the leading prognostic factor for mortality. The 5-year overall survival rates for women with tumor staging IIIA-IV was similar to the found in earlier studies based on different Brazilian cohorts [12-13]. These findings underline the urgent need for structuring services for early-stage breast cancer detection of women with inclusion criteria for screening. In Brazil, women aged 50-69 years have been encouraged to undergo mammography every 2 years, and to have their breasts examined by a physician from 40 years of age [14]. There is evidence of a 20% relative risk reduction for mortality with mammography at 11 years of follow-up [15]. However, inequalities in health service use in the Northeast Brazil disfavor a regular mammographic screening [16], which may lead in delay in diagnosis of breast cancer.

Despite evidence that young women with breast cancer have a worse prognosis compared to that of middle-aged women even if diagnosed early and receiving intense treatment [17-18], this study showed that age > 50 years was a predictive factor for mortality, which may be related to the delay in diagnosis, advanced-stage tumor, and less-than-standard treatment. In addition, age-related comorbidities may play a role in the survival rate in this

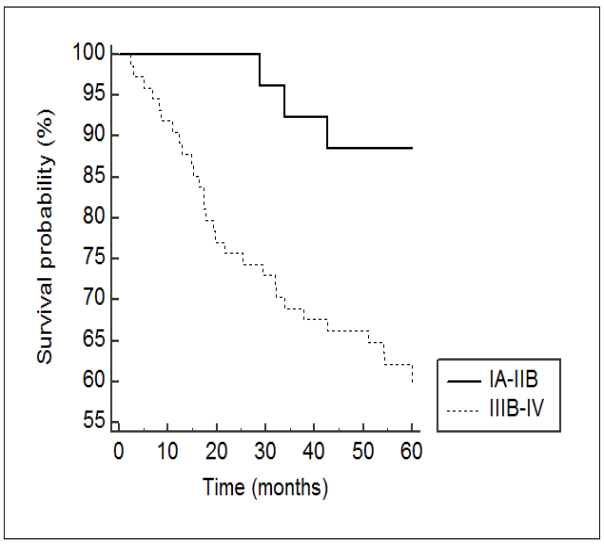

Figure 1. Kaplan-Meir Survival Estimates Based on TNM Stage at the Diagnosis

Table 1. Results of Log-rank Test and Multivariate Cox Regression Analysis of Clinical Factors in Predicting Overall Survival in Breast Cancer

Characteristic	Log-rank HR (95% CI)	p-value	Cox regression HR (95% CI)	p-value
Age (< 50 years vs. ≥ 50 years)	2.10 (1.06-4.16)	0.045	1.93 (0.91-4.07)	0.084
Relationship status (currently single vs. not currently single)	1.03 (0.52-2.06)	0.914		
Years of schooling (< 8 vs. ≥ 8)	1.00 (0.48-2.10)	0.993		
Income (< 2 minimum wages vs. ≥ 2 minimum wages)	1.32 (0.66-2.67)	0.421		
Residence (state city vs. principal city interior)	1.43 (0.71-2.85)	0.331		
TNM stage (IA-IIB vs. IIIB-IV)	4.34 (2.06-9.11)	0.008	3.41 (1.02-11.32)	0.046
Delay in first stage (yes vs. no)	2.18 (1.10-4.32)	0.027	1.87 (0.92-3.85)	0.086
Delay in second stage (yes vs. no)	0.76 (0.38-1.52)	0.44		
Delay in third stage (yes vs. no)	1.09 (0.55-2.17)	0.79		

HR, hazard ratio; CI, confidence interval.

Table 2. Results of Logistic Regression Analysis of Association between Clinical Factors and Death in Breast Cancer.

Characteristic	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Age (< 50 years vs. ≥ 50 years)	2.52 (1.04-6.09)	0.041	2.58 (1.00-6.67)	0.05
Relationship status (currently single vs. not currently single)	1.09 (0.47-2.53)	0.837		
Years of schooling (< 8 vs. ≥ 8)	0.98 (0.39-2.43)	0.963		
Income (< 2 minimum wages vs. ≥ 2 minimum wages)	1.40 (0.60-3.26)	0.435		
Residence (state city vs. principal city interior)	1.43 (0.60-3.43)	0.416		
TNM stage (IA-IIB vs. IIIB-IV)	5.23 (1.44-18.98)	0.012	3.99 (1.05-15.13)	0.042
Delay in first stage (yes vs. no)	2.76 (1.16-6.54)	0.021	2.57 (1.02-6.48)	0.046
Delay in second stage (yes vs. no)	0.68 (0.29-1.56)	0.359		
Delay in third stage (yes vs. no)	1.09 (0.48-2.52)	0.832		

OR, odds ratio; CI, confidence interval.

population. Unfortunately, the expression of predictive molecular biological markers for breast cancer prognosis and that are age-dependent were not evaluated and constitute an intrinsic limitation of study design.

Moreover, the present study found an association between the delay in seeking medical attention after self-discovering a potential breast cancer symptom and mortality. Patient delay maybe associated to health behavior, including lack of breast self-examination and general health care utilization, and socioeconomic factors such as old age and ethnicity. In addition, non-attribution of symptoms to cancer, fear of the disease and treatment and low educational level seem to be frequent causes of patient delay [19]. Interestingly, it has been showed that older women are more prone to procrastinate early detection of breast cancer resulting in more advanced disease and fewer a symptomatic cases [20]. Our findings highlight the need to strengthen actions for health education in primary health care and the implementation of an organized and permanent screening program for early detection of breast cancer.

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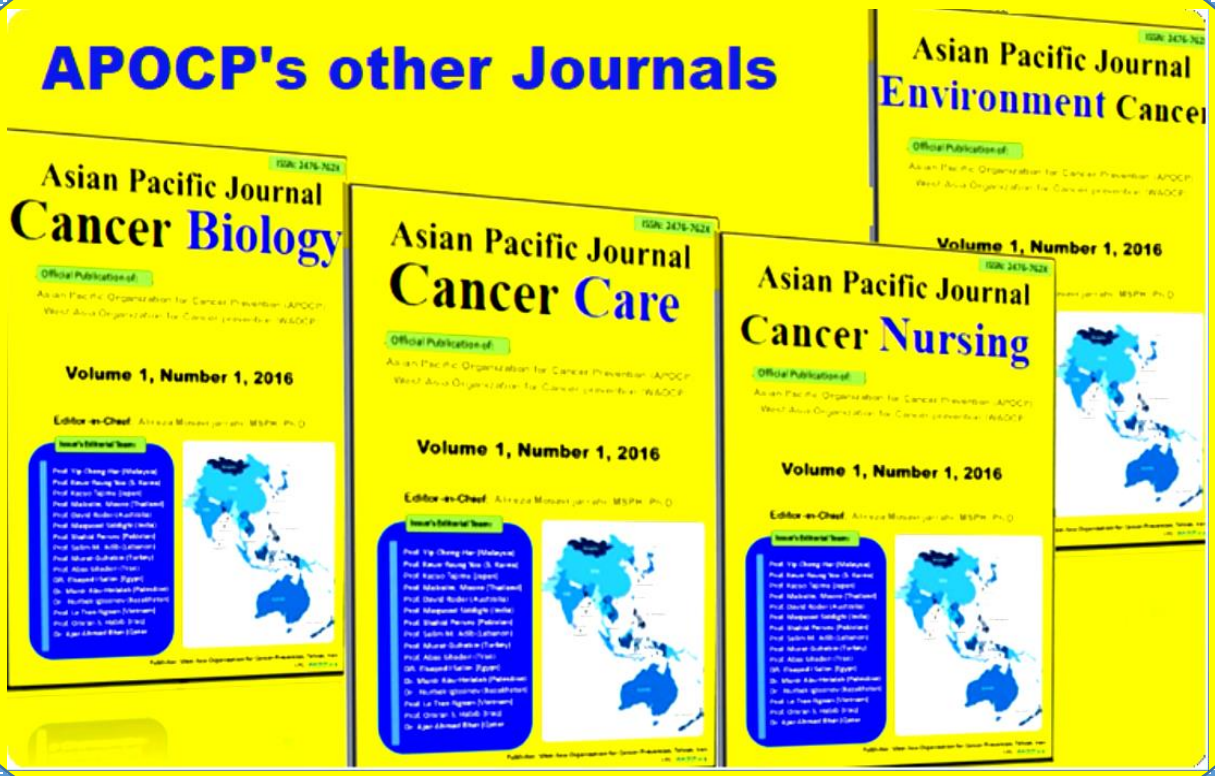

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