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Editorial

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Coagulopathy and Thromboprophylaxis in Patients with Cancer and COVID-19

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Coagulopathy such as venous thrombosis (VT) and pulmonary embolism (PE) has been recognized as one of the common and dreaded complications of COVID-19 infection.[1] It has been found to be nine times higher in COVID-19 patients as compared to non-COVID-19 patients. DIC or DIC like features have been found in 71.4% vs 0.6% COVID-19 non-survivors versus survivors.[2]

Cancer is a risk factor for coagulopathy like DVT, PTE and DIC. Therefore, COVID-19 infection makes this group of patients particularly vulnerable to severe disease with worse outcome. For this reason, cancer patients need special attention giving emphasis to thromboprophylaxis during this COVID-19 pandemic.

Different medical authorities like WHO, ASCO, ESMO, ASH, EMA and ISTH etc. have published guidance for the management of COVID-19 with or without cancer. In Bangladesh, DGHS, BSRO, HSOB have also published guidance for COVID-19 patient's management. Emphasis has been given for the diagnosis and thromboprophylaxis in all patients with highly suspected and confirmed COVID-19 patients.

Complete blood count, platelet count, PT, APTT, fibrinogen level, D-dimer level should be tested in all cancer patients with highly suspected or confirmed COVID-19. Thromboprophylaxis should be started, without delay, in all cancer patients having been suspected of COVID-19.

Low molecular weight heparin (LMWH) is the recommended anti-coagulant for COVID-19. It has some advantages over unfractionated heparin (UFH).[3] LMWH does not require routine monitoring neither it causes HIT. However, UFH should be used if CrCl is <30 ml/min. Heparin has anti-inflammatory effect that may be beneficial in addition to anti-coagulation. Direct oral anti-coagulants (DOAC) should not be used during active COVID-19 infection as thromboprophylaxis since its action may be affected by other drugs commonly used in COVID-19 infection e.g antiviral and/or azithromycin. However, DOAC may be convenient to use after post-COVID-19 thromboprophylaxis for selective patients.

Study has shown that thromboprophylaxis reduces the mortality of severe COVID-19.[4] This should also be true for cancer patients with COVID-19. Therefore, routine thromboprophylaxis should be considered in all hospitalized cancer patients with confirmed or highly suspected COVID-19.

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Original Article

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Profile of Geriatric Malignancies: A Five-Year Study

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Abstract

Objective: *The objective of this study was to find out the profile of geriatric cancers in National Institute of Cancer Research and Hospital, (NICRH), Dhaka during 2010 to 2014.* ***Methodology:*** *It was a retrospective study using hospital-based cancer registry records from January 2010 to December 2014. All geriatric patients with cancer, aged e" 65 years diagnosed by means of histological or cytological examination during that period and reported to cancer registry, were included in the study.* ***Results:*** *Per hospital cancer registry records, there were 43385 confirmed new cases attended NICRH during January 2010 to December 2014. Among which 8850 belong to geriatric group. The geriatric tumours comprised of 20.4% of all malignancies during theses 5 years time. Out of 8850 patients, 78.2% (n=6923) were male and 21.8% (n=1927) were female with a male to female ratio of 3.6:1. Around 73% (n=6463) of the patients were from young old group (65-74 yrs). About 45% (n=3977) of the patients were from Dhaka division and around 20% patients (n=1781) were from Chattogram division. More than 37% (n=2583) male patients were current smokers. In male patients lung was the leading site of cancer in each year followed by oesophageal cancer. Stomach cancer occupied the third place in each year except in 2011 where liver cancer took that position. Among female patients lung was the leading cancer in three successive years starting form 2011. In other two years cervical cancer led the tally. The other notable cancers in women were oesophageal cancer, breast cancer and lymphoma.* ***Conclusion:*** *In male the pattern is almost identical with that of the adult cancers. In female notable deviation was noted from usual adult female cancer as most of the years lung cancer led the tally.*

Key Words: *Cancer registry, geriatric malignancies, cancer profile*

Introduction

Ageing is a universal process observed in every living creature. Actually, it begins from intrauterine life, and continues up to death. Ageing induces many changes in physiological functions of organs, and systems. Nowadays, with the advent of new technologies, disease, and mortality rates have decreased, birth rates have dropped, as a result prolongation of life span occurred. The World Health Organization (WHO) defines old age as the period of life starting from 65 years of age.[1] According to WHO, in the year 2025 people aged 65 years and over will be expected to reach 800 million. [2]

Ageing is defined as irreversible structural and functional changes in molecules, tissues, organs, and systems of the body which become apparent with advanced age.

One of the predominant causes of mortality and morbidity is cancer whose incidence increases with age. Although cancer affects each age group nearly 60% of the cancer cases and 70% of the cancer related mortalities occur in individuals aged 65 or older. [3]

Global burden of cancer is increasing day by day. As a consequence of growing, and ageing population, an important part of this increase is predicted to concern developing countries like Bangladesh. Because of limitations in the application of screening programs, early diagnosis, and access to treatment, further increases in the incidence of cancer, and cancer-related mortality rates have been anticipated. [4, 5]

Materials and Methods:

We used five years hospital records in this retrospective study from January 2010 to December 2014. All geriatric patients with cancer, aged e" 65 years diagnosed by means of histological or cytological examination during that period who reported to the cancer registry of NICRH, were included in the study. The profile of geriatric cancer was studied focusing on the prevalence of tumors according to age, sex, residence and topography. Data were processed by editing and post-coding and analyzed by SPSS for Windows (IBM SPSS Statistics for Windows, version 25.0, Armonk, NY: IBM Corp.) software.

Results:

Per cancer registry data, there were 43385 confirmed new cases attended NICRH during January 2010 to December 2014. Among which 8850 belong to geriatric group (65 years or older). An average of 1770 cases attended per year. The geriatric tumours comprised of 20.4% of all malignancies during theses 5 years time. Out of 8850 patients, 78.2% (n=6923) were male and 21.8% (n=1927) were female with a male to female ratio of 3.6:1. Almost all were (93.9%) Muslim. Distribution of the geriatric patients by age group is shown in the table I.

Table I: *Distribution of the geriatric patients by age group*

Age group	Sex		Total n (%)
	Male n (%)	Female n (%)	
Year 2010			
65-74	1092 (69.7)	296 (73.8)	1388 (70.6)
75-84	397 (25.4)	96 (23.9)	493 (25.1)
85-94	67 (4.3)	8 (2.0)	75 (3.8)
=>95	10 (0.6)	1 (0.2)	11 (0.6)
Yea 2011			
65-74	862 (71.1)	302 (80.1)	1164 (73.3)
75-84	301 (24.8)	64 (17.0)	365 (23.0)
85-94	43 (3.5)	9 (2.4)	52 (3.3)
=>95	6 (0.5)	2 (0.5)	8 (0.5)
Year 2012			
65-74	818 (72.2)	224 (77.5)	1042 (73.3)
75-84	243 (21.4)	54 (18.7)	297 (20.9)
85-94	59 (5.2)	8 (2.8)	67 (4.7)
=>95	13 (1.1)	3 (1.0)	16 (1.1)
Year 2013			
65-74	950 (72.9)	221 (79.5)	1171 (74.1)
75-84	293 (22.5)	48 (17.3)	341 (21.6)
85-94	52 (4.0)	8 (2.9)	60 (3.8)
=>95	8 (0.6)	1 (0.4)	9 (0.6)
Year 2014			
65-74	1251 (73.2)	447 (76.8)	1698 (74.1)
75-84	370 (21.7)	109 (18.7)	479 (20.9)
85-94	69 (4.0)	23 (4.0)	92 (4.0)
=>95	19 (1.1)	3 (0.5)	22 (1.0)

Around 73% (n=6463) of the patients were from young old group (65-74 yrs). About 45% (n=3977) of the patients were from Dhaka division and around 20% patients (n=1781) were from Chattogram division. Least number of patients came from Rangpur (2.1%, n=188) and Sylhet (2.7%, n=236) divisions (Fig. 1). More than 37% (n=2583) male patients were current smokers whereas only 2.9% (n=55) female patients were current smokers (Fig. 2). In male patients lung was the leading site of cancer in each year followed by oesophageal cancer. Stomach cancer occupied the third place in each year except in 2011 where liver cancer took that position. Among female patients lung was the leading cancer in three successive years starting form 2011. In other two years, i.e. in 2010 and in 2014 cervical cancer led the tally. The other notable cancers in women were oesophageal cancer, breast cancer and lymphoma. Year wise five leading cancers are shown in table II.

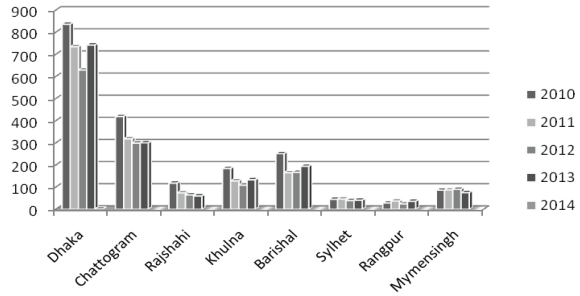

Figure 1: *Distribution of the geriatric patients by residence*

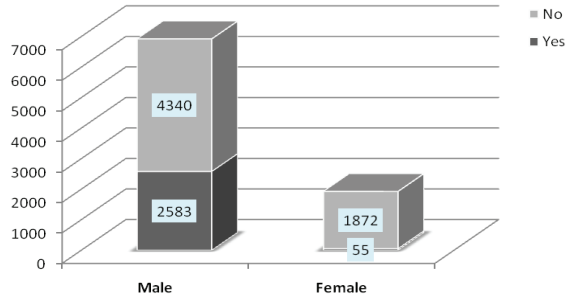

Figure 2: *Distribution of the geriatric patients by current smoking habit*

Table II: Year wise distribution of the geriatric patients by topography

	Male n (%)		Female n (%)
2010			
Lung	399 (25.5)	Cervix	35 (8.7)
Oesophagus	86 (5.5)	Oesophagus	30 (7.5)
Stomach	70 (4.5)	Lung	23 (5.7)
Prostate	49 (3.1)	Breast	16 (4.0)
Liver	45 (2.9)	Lymphoma	14 (3.5)
2011			
Lung	475 (39.2)	Lung	52 (13.8)
Oesophagus	82 (6.8)	Cervix	50 (13.3)
Liver	69 (5.7)	Breast	48 (12.7)
Stomach	61 (5.0)	Oesophagus	32 (8.5)
Lymphoma	32 (2.6)	Gall bladder	19 (5.0)
2012			
Lung	355 (31.3)	Lung	48 (16.6)
Oesophagus	88 (7.8)	Breast	32 (11.1)
Stomach	59 (5.2)	Oesophagus	30 (10.4)
Liver	41 (3.6)	Cervix	28 (9.7)
Prostate	40 (3.5)	Lymphoma	16 (5.5)
2013			
Lung	496 (38.1)	Lung	52 (18.7)
Oesophagus	93 (7.1)	Breast	43 (15.5)
Stomach	65 (5.0)	Lymphoma	43 (15.5)
Liver	56 (4.3)	Oesophagus	28 (10.1)
Lymphoma	43 (3.3)	Stomach	15 (5.4)
2014			
Lung	656 (38.4)	Cervix	96 (16.5)
Oesophagus	114 (6.7)	Lung	80 (13.7)
Stomach	79 (4.6)	Breast	57 (9.8)
Liver	66 (3.9)	Oesophagus	39 (6.7)
Prostate	53 (3.1)	Cheek /buccal mucosa	29 (5.0)

Discussion:

Like rest of the world, cancer is a public health problem with increasing importance in our country too. Prolongation of overall lifetime leads to increase in the older population in our country. As per World Bank report the life expectancy at birth in Bangladesh was 71.23 years in 2014.[6] The exact number or percentage of geriatric patients suffering from cancer is not known. In hospital cancer registry 2014 report of NICRH the proportional incidence among this group was reported as 20.6%. In the current study we found this rate as 20.4%. This percentage is more or less comparable with other countries rate. In Turkey, 27% of the patients diagnosed as cancer are aged 65 years and over.[3] In the United States of America more than 60% of the cancer cases are seen in old individuals aged 65, and over.[7]

In the current study the male to female ratio was 3.6:1. The exact cause of such male preponderance is not clear. Personal habits, social norms and history of occupational hazards could be the three important underlying factors. Further study in this regard is warranted.

In the current study about 45% (n=3977) of the patients were from Dhaka division. It does not necessarily mean that people of Dhaka division suffer more from cancer. Physical location of the institute might be playing role for this type of observation. Only well-designed population-based cancer registry can resolve such dilemma.

In our study lung was the leading site of cancer in each year among males. Lung cancer has the shortest survival times among other cancer types, and takes the lead among cancer- related deaths in the whole world (8). Half of the cases with lung cancer are diagnosed in the advanced stage. [8] In the USA, median age of newly diagnosed cases with NSCLC is 68 years, while 40%, and 14% of these cases are over 70, and 80 years of age, respectively (9). According to American Cancer Society (ACS) lung cancer is responsible from nearly 27% of all cancer-related deaths.[7] Owing to the decrease in the rate of smoking in Europe, and USA, decrease in incidence of lung cancer has been observed more frequently in men. Lung cancer -specific mortality rates between genders reflect smoking status, rates of quitting smoking, and historical differences within the last 50 years.[8] According to Globocan 2018 data published by International Cancer Agency, lung cancer ranks 2nd top position in men in Bangladesh. Similar trend was found in the European Union Countries, and in the USA. [8] In smokers the risk is higher relative to nonsmokers.[8]

In adult female breast cancer was the leading cancer.[10] But in elderly patients surprisingly lung cancer topped the tally in three successive years (2011-2013). Prolonged exposure to carcinogenic agents such as secondary smoking, DNA damage accumulation, tumor suppressor gene defects, impairment of cellular repair mechanisms, oncogenic activation, and attenuation of immunity have been held responsible for higher incidence of cancer in older individuals.[3] Since carcinogenesis is a very long process, emergence of cancer in advanced ages is a natural event.

In other two years cervical cancer out placed lung cancer. Both incidence, and mortality rates of invasive cervical cancer increases with age. Cervical cancer is a very costly disease which has a serious impact on health system, and population. In patients aged 65, and over cervical cancer has mortality rates ranging between 40, and 50%. However regular screening decreases cervical cancer risk at a rate of 80 percent.[8] Every year nearly 500.000 women are diagnosed as cervical cancer, and approximately 80% of them are seen in developing countries. [11]

Geriatric patients are not 'big' adult patients. Treatment, and care for older patients with cancer should be individualized rather than focusing on age of the patient. With comprehensive geriatric evaluation, risks, and benefits of the available treatment alternatives should be properly determined. Early diagnosis, treatment, and screening programs will be the key in decreasing incidence rates of cancer in elderly.

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Original Article

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Validity of Imprint Cytology in the Diagnosis of Ovarian Tumour

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Abstract:

A cross sectional study was performed for per operative evaluation of the ovarian tumour by imprint cytology and to correlate imprint cytology findings with histological findings as well as to determine and validate the diagnostic accuracy, sensitivity, specificity, positive predictive value and negative predictive value of imprint cytology in per operative differentiation of benign & malignant ovarian tumour. A total 250 patients were initially screened for and among them 50 patients were enrolled into the study according to the selection & exclusion criteria. In provisional diagnosis nearly two third (66%) patients presented with features of malignancy & suspicions of malignancy. In imprint cytology findings 42(84%) patients had benign and 8(16%) malignant. According to histopathology report a total of 41 patients had benign & 9 cases were malignant. In imprint cytology it was observed true +ve 8 cases, false +ve 0 case, false –ve 1 case & true –ve 41 cases as identified by histopathological report. The validity test of imprint cytology findings in the diagnosis of ovarian tumour had 88.9% sensitivity, 100% specificity, 98% accuracy, 100% PPV & 97.6% NPV. The findings of imprint cytology in the present study significantly correlate with histopathological diagnosis. Thus the clinical characteristics of ovarian tumour which raises the suspicion of malignancy can be further evaluated per-operatively by imprint cytology & this can help surgeon to adopt a rational approach in patient management.

***Keyword**: Imprint cytology.*

Introduction:

Ovarian carcinoma accounts for 3.0% of all female malignancy and 5th most common cause of death due to carcinoma in women in United States.[1] High incidence rates in the order of 10–12 per 100000 are found in Europe and in North America; the lowest rates below 3 per 100000 are from China and Africa.[2] The Age Specific Incidence Rate (ASIR) for ovarian cancer revealed that the disease increases from 35 years of age and reaches a peak between the ages 55-64 years. The trend analysis by period showed an increasing trend in the incidence rate of ovarian cancer in most of the registries, with a mean annual percentage increase in ASIR ranged from 0.7% to 2.4 %.[3] Cancer is one of the leading causes of morbidity and mortality in Bangladesh. Because of lack of cancer registry, the exact estimate of

incidence and death from ovarian cancer cannot be stated. But various studies done on cancer patients reflects high incidence and mortality. The estimated cancer load is 1.2 million with an incidence of 2,00,000, a prevalence of 8,00,000, and mortality at 1,50,000.[4] Cytology is being used for many years to diagnose and differentiate the types of tumours. Thus, cytology provides useful information preoperatively to plan judicious treatment. But cytology is not without limitations. Elucidation of cytologic specimens requires detail conception on morphological patterns along with perception of the limitations of procedure. Along with several diagnostic methods like USG, Tumor associated antigens as CA-125, CT scan, MRI, PET-CT, image guided fine needle aspiration cytology (FNAC) of ovarian masses is an efficient diagnostic modality for accurately diagnosing ovarian tumours prior to surgery. It is used both for primary diagnosis of ovarian lesions and follow up of recurrent malignancies. But FNAC has its limitations. Owing to the complexity and wide spectrum of ovarian diagnosis, FNAC may not always accurately corroborate with the histopathology. In addition, border line epithelial tumours may be difficult to interpret on aspiration cytology. This needs adequate training and experience on cytology. Thus, accuracy of FNAC is dependent on correlations with clinical parameters, serum tumour markers and USG. Frozen section (FS) plays an important role in intraoperative diagnosis of ovarian tumour, chiefly to determine whether it is benign or malignant. Limitations of Frozen section need to be taken into consideration in order to avoid great mistakes that will be detrimental to patient management. These limitations can be divided into three main categories, namely sampling error, technical problem and interpretative error. Moreover, FS is not available in most centers as the test involves the use of expensive cryostat machine and expert hand technician is needed. Imprint cytology is an intra-operative procedure that can provide rapid and reliable diagnosis of ovarian tumour with careful interpretation of results by an expert histopathologist. This is a simple procedure where smears are prepared on glass slides from multiple sites. The method is inexpensive and does not require special instruments and trained technician. Imprint cytology is helpful in differentiation between neoplastic and inflammatory conditions.[5] It is also beneficial for confirmation of recurrent malignancies. To determine the clearance or involvement of surgical margins and lymph nodes.[6] Imprint cytology of the tumour at the time of surgery is important to plan the treatment strategies. Thus, many aggressive surgeries can be avoided specially in young reproductive age group women. Riaz et al. (2015) found the sensitivity and specificity of imprint cytology to be 93% and 83.3% respectively in diagnosing ovarian tumour.[7] In another study in India, by Das et al. (2014) imprint cytology had 94.0% sensitivity, specificity 74% and positive and negative predictive value of 63% and 96% respectively as well as the diagnostic accuracy of 78.0% in diagnosing ovarian tumour.[8] In our country a study was done by Dr. Bidoura Naznin and observed the combined diagnosis of FS and IC and compared it with histopathological diagnosis. She found diagnostic accuracy, sensitivity, specificity, PPV and NPV of 99.8%, 98.46%, 100%, 100%, & 95% respectively. [9]

Imprint cytology as a diagnostic procedure have some limitations. The depth of infiltration cannot be analyzed with imprint cytology and Tumours which are well-differentiated but with dense fibrous stroma cannot be interpreted through this method.[10] In spite of all its advantages and diagnostic accuracy imprint cytology is under-utilized. It may be a better evaluating option for diagnosing ovarian tumour when compared with other sophisticated complex technique such as FS. There are very few studies done on ovarian tumour using imprint cytology in Bangladesh. Therefore, this study is intended to evaluate the validity of imprint cytology in the diagnosis of ovarian tumours and compare it with histopathology which is the gold standard.

Materials and methods:

This cross-sectional study was carried out on patients with ovarion tumour, who were admitted in the Department of Obstetrics and Gynaecology in collaboration with Department of Pathology, Sir Salimullah Medical College, Dhaka, of the same hospital during the study period from April 2016 to March 2017. 50 patients were enrolled having inclusion criteria with ovarian tumour who are diagnosed by history, clinical examination and investigations as well as tumours wich are resectable and the exclusion criteria with unfit for surgery because of severe comorbidities, patients with unresectable ovarian tumours, Patients with past history of major pelvic surgery for non-ovarian pathology-

fibrosis, vascular changes and anatomical distortion of pelvic organs and Patient who refused to participate in the study. Per operative imprint smares were prepared from fresh ovarian tissue. After bisecting the lesion, the surface was mopped dry of fluid or blood, to facilitate adhesion of the cells to the surface of glass slide. The suspicious area was identified, then clean and dry glass slides were touched firmly to the cut surface without undue pressure. The imprinted slides were immediately fixed in 95% ethanol and sent to the laboratory. After proper processing of the representative sections, slides were stained with Haematoxylin and Eosin stain. The slides were then seen under light microscope. The results of imprint cytology were printed instantly. The specimen of ovarian tumour which was removed from the body immerged in 10% formalin and sent to laboratory for histopathology report. Histopathological categorization was done according to WHO classification. The results of imprint cytology and histopathology report were lastly included in the data collection sheet. Data were analyzed by SPSS for Windows (IBM SPSS Statistics for Windows, version 20.0, Armonk, NY: IBM Corp.) software. The results were presented in tables, figures, diagrams. For the validity of study outcome, sensitivity, specificity, accuracy, positive predictive value and negative predictive value of imprint cytology in the discrimination of the benign and malignant ovarian tumours mass was calculated out after confirmation of the diagnosis histopathologically.

Results:

The mean age was found 36.8±12.0 years with ranged from 12 to 70 years. In provisional diagnosis nearly two third patients present with feature of benign ovarian tumour and one third present with feature of malignancy and suspicious of malignancy. In Imprint cytology findings 45(90.0%) patients had benign, 4(8.0%) malignant and 1(2.0%) had suspicious. According to histopathology, a total 41 patients had benign and 9 cases malignant. In imprint cytology it was observed, true positive 8 cases, false positive 0 case, false negative 1 case and true negative 41 cases are identified by histopathological finding. The validity test of imprint cytology findings in the diagnosis of ovarian tumour had 88.9% sensitivity, 100.0% specificity, 98.0% accuracy, 100.0% positive predictive value and 97.6% negative predictive value.

Table I: *Comparison of imprint cytology findings with Histopathological finding*

Imprint cytology findings	Histopathological finding		Total
	Malignant	Benign	
Malignant/ Suspicious	8(true positive)	0(false positive)	8
Benign/ Suspicious	1(False negative)	41 (true negative)	42
Total	9	41	50

Imprint cytology findings, true positive 8 cases, false positive 0 cases, false negative 1 case and true negative 41 cases are identified by histopathological finding.

Table II: *Validity of imprint cytology with histopathological findings.*

Validity test	Imprint cytology findings (%)
Sensitivity	88.9
Specificity	100.0
Accuracy	98.0
Positive predictive value	100.0
Negative predictive value	97.6

The table shows the validity of imprint cytology when compared with histopathological findings which is considered as gold standard. After calculating sensitivity, specificity, accuracy, positive predictive value, negative predictive value, it was observed 88.9%, 100%, 98%, 100%, and 97.6% respectively.

Discussion:

One of the most important predictors of malignancy is the age of the patient. The risk of malignancy in ovarian tumors increases 12-fold from the ages 12-29 years to

60-96 years.[11] Ovarian malignancy is a serious disease, affecting women of all ages, more so above 50 years.[12] In this present study, it was observed that 40.0% patients belonged to age 31-40 years. The mean age was found 36.8±12.0 years with ranged from 12 to 70 years. Riaz et al.[8] found 62.0% patients were above 40 years with ranged from 10 to 70 years. Das et al.[9] mentioned that serous cystadenocarcinoma occurred a decade later than the benign neoplasm. The benign mucinous neoplasms were predominant in 11 to 30 years and malignant mucinous neoplasms were most commonly found in 41 to 50 years age group. Granulosa cell tumour was common in the age group of 41 to 50 years which was similar to the observation made by Young et al.[13] The higher age range may be due to increased life expectancy, geographical variations, racial and ethnic differences, genetic causes and different lifestyle have significant impacts to developed ovarian masses. In this current study, it was observed that majority (98.0%) patients had unilateral USG findings. Almost half (46.0%) patients belonged to size of mass d"10 cm^2. More than two third (70.0%) patients had cystic consistency. One (2.0%) patient had locularity. Bandyopadhyay et al.[14] mentioned in their study that USG revealed 28.4% solid tumors, 48.6% partly solid and partly cystic tumors and 23.0% cystic tumors. In this current study, it was observed that the mean serum CA-125 level was found 241.7±114.2 mIu/ml with ranged from 5 to 465 mIu/ml. Mean serum CA-19-9 level was found 15.9±14.8 mIu/ml with ranged from 1.0 to 72.3 mIu/ml. Mean serum CEA was found 1.7±0.2 mIu/ml with ranged from 1.4 to 1.8 mIu/ml. Kudlacek et al.[15] observed 79.0% of all ovarian cancers are positive for CA 125. Most widely used tumor marker in ovarian carcinoma, often considered the gold standard is CA 125. It is raised in 90% of ovarian epithelial cancer. In Das et al.[9] study preoperative serum levels of CA125 were obtained from all 50 cases of which CA 125 level was elevated in 38.0% cases. In this present study it was observed that the validity test of imprint cytology findings had diagnosis sensitivity 88.9%, specificity 100.0%, accuracy 98.0%, positive predicative value 100.0%, and negative predicative value 97.6%. In our country Bidoura (2009), found imprint cytology technique diagnostic accuracy, sensitivity, specificity, positive predictive value and negative value were obtained as 91.67%, 92.31%, 89.47%, 96.77% and 77.27% respectively. [9] Upreti (2000), a study done in BSMMU revealed the similar accuracy, sensitivity, specificity, PPV and NPV (98.9%, 100%, 98.8%, 93.7% & 100%) respectively, which were almost similar to the present study. [16]

Conclusion :

This study was done to establish diagnostic value of imprint cytology in per operative evaluation of ovarian tumour. The histopathological diagnosis of ovarian tumour in the present study significantly correlated with imprint cytology findings, and the validity tests are almost identical as observed by many investigators. The clinical characteristics of the ovarian tumour those give suspicion of ovarian malignancy and is evidenced by imprint cytology per-operatively & thus can help the gynaecologists in the rational approach of patient management by keeping the facility of imprint cytology in the operation theatre. Imprint cytology is a less expensive, simple, fast and reliable method for diagnosis of various ovarian neoplasms.

Conflict of interest: None declared.

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TURBT under Spinal Anesthesia: A Comparative Study of Outcome between Anatomical Landmark Guided and Ultrasound Guided Obturator Nerve Block

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Abstract:

Transurethral resection of urinary bladder tumors (TURBT) produces adductor muscle contraction from obturator nerve stimulation (obturator jerk) that may interfere complete resection and may cause perforation of urinary bladder. This reflex can be avoided by obturator nerve block (ONB). The key objective of this study was to compare the occurrence of obturator jerk and the ability to complete the resection of bladder tumor by anatomic landmark-guided and ultrasound (USG) guided obturator nerve block (ONB). In this quasi-experimental study 125 cases of urinary bladder tumor of 5 cm or less were included. Sixty eight cases were in landmark group (Group A) and 57 cases were in ultrasound guided group (Group B).Outcomes of two groups were compared. No jerk or mild jerk was taken as success where as severe jerk was taken as failure. In our study success rate was 94.11% in group A and 98.24% in group B. The only complication was small blood vessel puncture (blood aspirate) in 7.35% cases in group A. In conclusion, the outcomes in both the groups were identical. So anatomical landmark guided ONB can safely be practiced where ultrasound guidance is not available.

Key wards: *Obturator jerk, TURBT, Urinary bladder tumor.*

Introduction:

Transurethral resection of urinary bladder tumors (TURBT) produces adductor muscle contraction from obturator nerve stimulation (obturator jerk) that may cause perforation of urinary bladder. This reflex can be avoided by obturator nerve block (ONB). The obturator nerve is derived from the 3rd and 4th lumbar nerves with a minor contribution from 2nd lumber (L2) The nerve descends on psoas muscle and lies deep in obturator canal (which is bordered by the obturator membrane, obturator muscles, and superior pubic ramus) from which it exists and divides into anterior and posterior

branches. Anterior branch gives rise to articular branch to hip and innervates adductor muscles, whereas the posterior branch innervates deep adductor muscles and knee joint.[1] The obturator nerve along with vessels pass from pelvic cavity where it runs close to prostatic urethra, bladder neck, and inferolateral bladder wall and exit to thigh through canal where it can be easily blocked.[2] The key objective of this study was to compare the occurrence of adductor jerk and the ability to complete resection of bladder tumor by anatomic landmark-guided and ultrasound (USG) guided obturator nerve block (ONB).

Materials and Methods:

Study design: This was a quasi-experimental study.

Study procedure and anesthetic technique: One hundred twenty five patients with age range 30–70 years of the American Society of Anesthesiologists Class I–IV scheduled for elective urinary bladder tumor resection under subarachnoid block (SAB). Samples were purposively divided into two groups in this study. Both the groups received 10 ml 2% preservative free lignocaine. The drugs were given as per the groups: Group A: The drug was injected 1.5cm lateral and 1.5 cm caudal from pubic tubercle (PT). Group B: Ultrasound-guided injection of local anesthetic into the interfascial plane between the pectineus and obturator externus muscles to blockade both the anterior and posterior branches of the obturator nerve. Preoperative assessment included ultrasonography of the urinary bladder to decide the side to which obturator nerve was to be blocked.

An intravenous line was secured and patients were monitored for heart rate, noninvasive blood pressure, and oxygen saturation. All patients after aseptic preparation received subarachnoid block by anesthesiologist. After the completion of the block, patients were laid in the supine position and subsequently waited for 5 min for fixation of drug and assessed for sensorimotor block. Further procedure was performed as per the group allocation. Antiseptic preparation of the groin area was done.

In Group A, the pubic tubercle was identified by palpation, a 1.5-cm long horizontal line is drawn laterally from pubic tubercle (Line A) then from this point another 1.5 cm vertical line is drawn (Line B) caudally. The injection insertion point is labeled at the tip of the end of the vertical line (Line B). A 10CC syringe with 10 ml 2% lignocaine was inserted perpendicularly and the needle is advanced until it makes contact with the inferior border of the superior pubic ramus at a depth of 2–4 cm. During the second phase, the needle is slightly withdrawn and then slipped along the anterior pubic wall then the needle was advanced further 2-3 cm. Then negative suction was done to confirmthat needle tip is outside of any blood vessels.

In the group B, ultrasound-guided injection of local anesthetic into the interfascial plane between the pectineus and obturator externus muscles successfully produces blockade of both the anterior and posterior division of the obturator nerve.

For both the groups, a waiting period was 5 min was allowed for the full effect of the block and then resection was allowed to perform.Monopolar cautery was used to resect the tumor.

Obturator jerk was defined as jerky adduction and internal rotation of the thigh at hip joint during the operative procedure. Outcome was taken as success for “no jerk” and “mild jerk” groups, where complete TURBT could have been done, and failure was taken for “severe jerk” group.

Results:

Of the 125 patients included in this study, age ranges from 30 year to 70 year. Male female ratio was 3:1. Only lateral wall tumors of d”5 cm size were included in this study. In landmark guided group any sorts of jerk was absent in most of the case (59, 86.8%). This percentage was even higher in USG guided group (54, 94.3%). Mild jerk was present in five cases (7.4%) in group A patients while two patients (3.5%) of group B experienced the same jerk. In group A, four (5.9%) patients had developed severe jerk while only one patient (1.8%) in group had such jerk (Fig. 1). We considered mild or no jerk as success and severe jerk as failure. So, most of the patients in both groups (64 and 56 in group A and group B respectively) experienced successful block and hence the difference was not statistically significant (p>0.05) (Table 1). Group B i.e. USG guided group patients did not develop any complication during the procedure but group A i.e. landmark guided group patients experienced five (7.4%) small vessels punctures (Table 2).

Table - I : *Effectiveness of block*

Effect	LM guided (group A) n=68 n (%)	USG guided (group B) n=57 n (%)	Fisher's Exact test	*p*-value
Success	64 (94.1)	56 (98.2)	0.687	0.241
Failure	4 (5.9)	1 (1.8)		(NS)

Table-II : *Complications of block*

Complications	LM guided (group A) n=68 n (%)	USG guided (group B) n=57 n (%)
No complication	63 (92.6)	57 (100)
Small vessels puncture	5 (7.4)	0 (0.0)

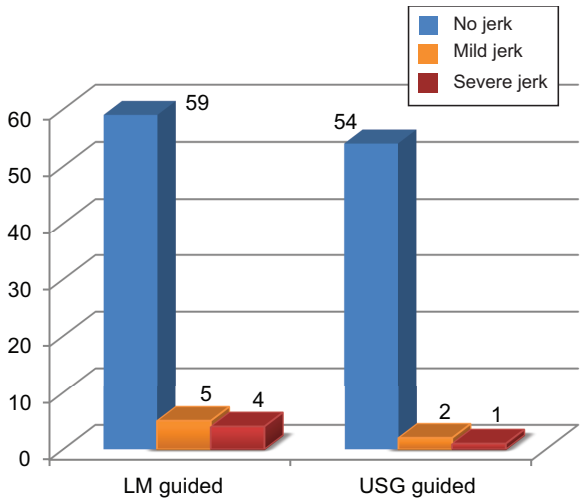

Fig.-1: *Comparison in jerks in two modalities.*

Discussion:

TURBT is used for surgical treatment of non-muscle invasive bladder cancer. It cannot be carried out effectively in lateral bladder wall tumors due to stimulation of obturator nerve. That lies at lateral wall of bladder and easily get stimulated by the electrical current passed through the loop during resection with an intense involuntary response from adductors (adductor longus, brevis, magnus, gracilis) and internal rotation (obturator externus) of hip called obturator jerk. It produces urinary bladder wall perforation and tumor cell spillage. It may also produce blood vessel injury and life threateninghemorrhage. Ultimate outcome is oncologically compromised resection and laparotomy. [3]

Several methods have been used to avoid the jerk such as reducing the diathermy power, using bipolar instead of monopolar cautery or using general anesthesia but none has been completely successful.

Venkatramani et al.[4] compared monopolar with bipolar cauterization for TURBT and concluded that bipolar TURBT was not superior to unipolar TURBT with respect to obturator jerk, bladder perforation, although Gupta et al.[5] eliminated nerve stimulation with the use of current of power as low as 50 W and 40 W for cutting and coagulation, but these settings have been reported to be too low for satisfactory resection.

Various other strategies, such as partial filling of the bladder during resection, modification in the surgical procedure such as resecting the tumor on thinner slices, laser resection, reverse in polarity of electric current, change in site of inactive electrode and using general anesthesia with muscle relaxants, have been adapted to avoid complications during TURBT but with wide-ranging achievements. [6, 7] Laser systems are luxurious and not easily available at many centers. General anesthesia is not a suitable option as it is associated with pulmonary complication which is so prevalent in the old age group.

Various methods have been described in literature to block obturator nerve. Prentiss et al.[8] in a study have reported that the use of sonography is associated with higher success rates of 97.2% in ultrasound-guided ONB procedures which is comparable with our study (98.2%).

According to Augspurger and Donohue [9] success of abolishing obturator jerk with anatomic landmark guided approach was 83.8% but in our study it is 94.11%.

Kuo [10] and Khorrami et al. [11] described the transvesical blockade of obturator nerve with 10 ml 1% lignocaine injected through cystoscope along with spinal anesthesia (thirty patients) and compared it with spinal anesthesia only group (thirty patients). In the intervention group, 34 ONB were performed. They observed a significant jerk in the control group (16.5%) compared to the intervention group (3%). In our study, severe jerk was occurred 5.9% in group A and 1.8% in group B.

Malik et al. [12] reported transfusion in 25% of patients (11/42) after TURBT. In our study, no group needed blood transfusion due to vessel injury. During needle insertion for ONB 7.4% cases blood vessels were punctured that could have been managed by withdrawing of needle and pressure application by thumb. None could have developed hematoma at injection site. No bladder perforation or obturator neuropathy occurred in this study.

Conclusion:

Anatomical landmark guided ONB is a safe and effective method to avoid obturator jerk which may occur in TURBT under SAB. It is easy to administer and can safely be practiced where ultrasound guidance is not available.

Conflict of interest: No conflict of interest.

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Original Article

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Socio-Demographic Factors of Stomach Cancer Patients Admitted in NICRH

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Abstract

Background: *Gastric cancer is the 4th most common cancer worldwide and the second most common cause of cancer related deaths. The available treatment modalities are not satisfactory in terms of overall survival benefit. Therefore, primary prevention and early detection strategies remain the most important public health interventions. The aim of the study was to determine socio-demographic factors of stomach cancers among the patients admitted in NICRH.* ***Methods:*** *It was a cross-sectional comparative study conducted at the department of medical oncology of NICRH. A total of 122 patients suffering from different cancers were included in the study.* ***Results:*** *The mean age of the gastric cancer patients was 51.8 (±12.28) years and that of the non gastric cancer patients was 51.43 (±12.09) years. Most of the patients came from Dhaka & Chattogram divisions. In gastric cancer patients just less than half of the respondents (44.3%) had no education and 31% of the respondents can sign their name only. Most of the gastric cancer patients were suffering from intestinal variant (45, 73.8%) and the rest 16 (26.2%) patients had diffuse type.* ***Conclusion:*** *Anti-salt and spicy food intake campaign should be started. Through awareness program people should be encouraged to moderate exercise & to take more vegetables and fish.*

Key words*: Stomach cancer, Risk factors*

Introduction

Gastric cancer is the 4th most common cancer worldwide and the second most common cause of cancer related deaths.[1] Despite complete resection of gastric cancer and lymph nodes dissection, as well as improvement of chemotherapy and radiotherapy, there are still 700000 gastric cancer related deaths per year worldwide and more than 80% of patients with advanced gastric cancer die of the disease or recurrence of the disease within 1 year after diagnosis. None of the treatment modalities we have been applying today can influence the overall survival rates. At present, the 5-year relative survival rate for gastric cancer is about 28%.[2] According to the International Gastric Cancer Society, more than 800,000 people are affected by gastric cancer every year and up to 650,000 people have succumbed to gastric cancer.[2]

It is likely that in 2020 gastric cancer will increase by 10% in developing countries. Gastric cancer remains an important burden for public health, particularly in less developed countries including Middle and Eastern Asia, South America and Eastern Europe, being responsible for 70% of cases worldwide.[2] Mortality rates remain high with disease usually detected late in its course; at this stage treatment strategies are often not useful. Therefore, primary prevention and early detection strategies remain the most important public health interventions.[3] However, these strategies require identification& understanding risk factors that lead to carcinogenesis. With gastric cancer, a disease that is traced to ancient civilizations, the risk appears to evolve over time as a possible result of change in dietary and lifestyle factors. Improved sanitation, refrigeration and effective screening strategies have led to significant reduction in incidence of cancer in the recent past but the fact that this disease remains prevalent in modern times suggests that other environmental risk factors are involved in sustaining this condition. Salt is strong independent risk factors for gastric cancer whereas alcohol is only a risk when it is heavily consumed. Red meat and high fat increase the risk of gastric cancer while fresh fruits, vegetables (allium family) and certain micronutrients (selenium, vitamin C) reduce the risk with evidence lacking for fish, coffee and tea. Obesity is increasingly recognized as a contributory factor in gastric cardia carcinogenesis. Therefore, modest daily physical activities can be protective against cancer. Large epidemiological studies have shown a correlation between diet and gastric cancer development.[4] In particular, pickled foods, foods rich in nitrites, and diet poor in fruits and vegetables are reported to increase the risk of gastric cancer.[5] An earlier study examined 24-hour urine samples from 39 populations, sampled from 24 countries and showed a correlation between gastric cancer development and nitrate consumption and salt expulsion.[6] Similarly, several studies have demonstrated that while a diet rich in foods fried in fat, processed meat and fish, alcohol and animal fats increases the risk of gastric cancer, consumption of fresh fruits and fish reduces that risk.[7] One earlier study suggested a positive correlation between gastric cancer risk and nitrate-based fertilizer[7], salted products containing nitroso compounds and smoked meats.[7] On the other hand, due to its antioxidant capacity, black tea might have anticarcinogenic properties[8], and indeed, a recent study suggests that black tea consumption might lower the risk of cancer development. Gender is shown to play a role in the occurrence of certain cancers. Gastric cancer is more frequent among males than females as a whole. Other factors also play a considerable role in the development of gastric cancer, similarly as in various other cancer types. For example, factors such as low socioeconomic level, excessive tea drinking, eating salted foods, living on a diet poor in fruit and vegetables, living in poor hygiene conditions, consuming excessively hot foods and spring water might trigger the development of gastric cancer.[9] Study was to determine environmental and dietary factors that might induce the development of gastric cancer, most frequently encountered type of gastrointestinal system cancer in Bangladesh.

Materials and methods

It was a comparative cross-sectional study carried out in National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka from January 2017 to March 2018. The subjects were selected purposively. The targeted sample size was 61. Equal numbers of other patients not suffering from gastric cancer were also included in the study for comparison. After obtaining appropriate permission data were collected by researcher from the patients by face to face interview. Relevant medical records were consulted and recorded in a semi-structured questionnaire.

Results

Out of 122 patients 61 patients were suffering from gastric cancers. Another 61 patients of non-gastric cancers (lung cancer 17, 27.9%, lymphoma 15, 24.6%, sarcoma 11, 18%, seminoma 9, 14.7%, cervical cancer 5,8.2% and other cancers 4, 6.6%) were also enrolled in the study. The mean age of the gastric cancer patients was 51.8 years and that of the non gastric cancer patients was 51.43 years (Fig. 1A, IB). No significant difference was observed between these two groups ($p>0.05$). Most of the patients came from Dhaka & Chattogram divisions (Fig. IC). There were 48 (78.7%) male and 13 (21.3%) female gastric patients in the current study. Almost similar numbers of male (50, 82%) and female (11, 18%) non-gastric cancer patients were included in the study. Statistically the difference was not significant ($p>0.05$) (Table I). Most of the respondents in both groups were

doing some services (75.4% in GC group and 68.9% in non-GC group). Almost equal numbers of respondents in both groups were day laborer (11.5% in GC group and 9.8% in non-GC group). Only few respondents in both groups were business person or students. The differences of occupation between two groups was not statistically significant (p>0.05) (Table I). In gastric cancer patients just less than half of the respondents (44.3%) had no education and 31% of the respondents can sign their name only. Only 23% of the respondents in this group had primary level education. In non-gastric cancer patients group only 8.8% respondents were illiterate but a considerable percentage (42.6%) had primary level education. The differences of education between these two groups were statistically significant ($\div^2$ =33.169 (df=4); I<.001). Most of the gastric cancer patients (39.3%) were earning BDT 5000-10000 per month while most of the non-gastric cancer patients (45.9%) were earning BDT 10000-20000 per month. A considerable numbers of patients in both groups were earning <5000 BDT per month. However, the differences of monthly income between these two groups were statistically not significant ($\div^2$ =4.66 $_{(df=3)}$; p>0.05). Around 57% patients of GC group were using well maintained sanitary latrine while this figure was 77% in non-GC patients group. In former group more patients were using poorly maintained or open latrine than latter group. The differences of latrine types between these two groups were statistically significant (p<0.05) (Table I). Fourteen patients in GC group had blood group "A" while only 6 patients of non-GC group had "A" group blood. "B" blood patients were higher in non-GC group. However, this difference was statistically not significant (p>0.05) (Table II). Only 5 GC patients had gastric cancer in their family and 7 had family members with other cancer. These numbers in non-GC patients were 4 and 8 respectively. The differences were not statistically significant (Table II). Most of the gastric cancer patients were suffering from intestinal variant (45, 73.8%) and the rest 16 (26.2%) patients had diffuse type (Fig. ID).

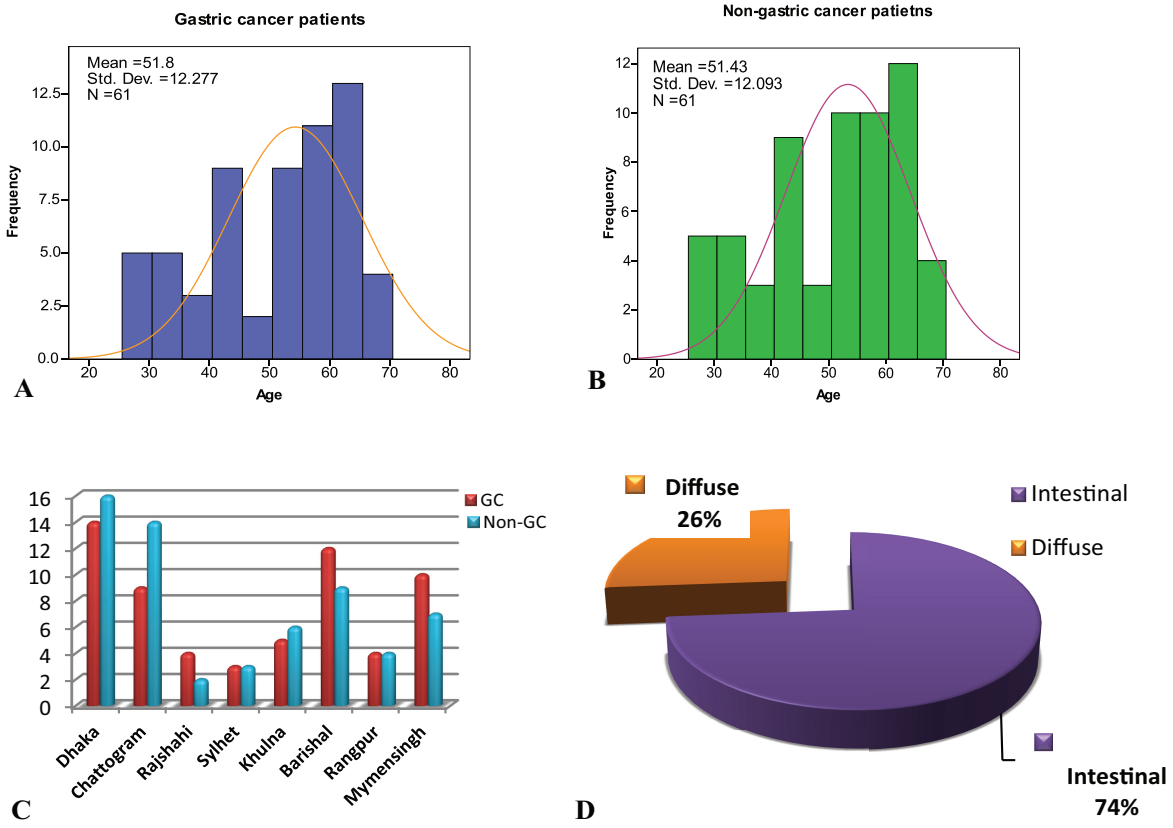

Figure 1: ***A)*** *Age distribution of the gastric cancer patients* ***B)*** *Age distribution of the non-gastric cancer patients* ***C)*** *Distribution of the patients by division* ***D)*** *Histological types of the gastric cancer*

Table I: *Distribution of the respondents by occupation*

Parameter	Category		$\chi 2$	*p*-value
	GC(n=61)	Non-GC(n=61)		
Gender				
Male	48 (78.7)	50 (82.0)	0.207	0.649
Female	13 (21.3)	11 (18.0)		
Occupation				
Service	46 (75.4)	42 (68.9)	10.612	0.069*
Day laborer	7 (11.5)	6 (9.8)		
Business	4 (6.6)	5 (8.2)		
Student	2 (3.3)	3 (4.9)		
Unemployed	2 (3.3)	5 (8.2)		
Educational status				
Illiterate	27 (44.3)	5 (8.2)	33.169	<0.001
Can sign only	19 (31.1)	16 (26.2)		
Primary	14 (23.0)	26 (42.6)		
SSC	1 (1.6)	11 (18.0)		
HSC	0 (0.0)	3 (4.9)		
Family income (BDT)				
<5000	17 (27.9)	15 (24.6)	4.66	0.188*
5000-10000	24 (39.3)	16 (26.2)		
10000-20000	19 (31.1)	28 (45.9)		
>20000	1 (1.6)	2 (3.3)		
Sanitation				
Open place	5 (8.2)	0 (0.0)	7.997	0.011*
Poorly maintained place	21 (34.4)	14 (23.0)		
Well maintained place	35 (57.4)	47 (77.0)		

*Fisher's Exact test; GC= Gastric cancer; Percentage is given in parenthesis

Table II: *Distribution of the patients by blood group and family h/o cancer*

Variables	Category		χ^2	*p*-value
	GC (n=61)	Non-GC (n=61)		
ABO blood group			4.058	0.255
AB	7 (11.4)	8 (13.1)		
A	14 (23.0)	6 (9.8)		
B	25 (41.0)	27 (44.3)		
O	15 (24.6)	20 (32.8)		
Family H/O gastric cancer				
Yes	5 (8.2)	4 (6.6)	0.12	0.729*
No	56 (91.8)	57 (93.4)		
Family H/O other cancer				
Yes	7 (11.5)	8 (13.1)	0.076	0.782
No	54 (88.5)	53 (86.9)		

*Fisher's Exact test; GC= Gastric cancer; Percentage is given in parenthesis

Discussion

Gastric cancer remains an important burden for public health, particularly in less developed countries including Middle and Eastern Asia, South America and Eastern Europe, being responsible for 70% of cases worldwide.[2] Mortality rates remain high with disease usually detected late in its course; at this stage treatment strategies are often not useful. Therefore, primary prevention and early detection strategies remain the most important public health interventions.[3] However, these strategies require identification and understanding of risk factors that lead to carcinogenesis. With gastric cancer the risk appears to evolve over time as a possible result of change in dietary and lifestyle factors. Improved sanitation, and effective screening strategies have to lead to significant reduction in incidence of this cancer in cancer in the recent past [10] but the fact that this disease remains prevalent in modern times suggests that other environmental risk factors are involved in sustaining this condition. In the present study the overall sanitation status was significantly worse in the houses of gastric cancer patients.

Gastric cancer tends to affect the poorer classes. Although the reasons are not exactly known, some investigators suggest this may be the result of excessive physical activity, exposure to high risk occupation and having poorer quality diets in comparison to the wealthy.[10] However in our study no significant difference was noted regarding family income. In a case-control study in Brazil a reverse association was found with an index of socio-economic status i.e. educational status. [11] The present study also supports this finding.

Conclusion

No significant differences were noted between gastric cancer and non-gastric cancer patients in respect to age, sex, area of residence, occupation and family income. Likewise ABO blood grouping and family history of cancer were not found to be associated with gastric cancer. However level of education and low sanitary conditions were found to be associated with the development of gastric cancer.

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Case Report

Cancer J Bangladesh 2020;1(1): 22-25
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Malignant Phyllodes Tumor of the Breast Metastasized to the Forearm-A Case Report

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Abstract

Background: *Malignant phyllodes tumors are relatively rare, accounting for 0.3% to 0.9% of all tumors of the breast. These tumors metastasize approximately 20% of the cases depending upon the histologic behavior. The most common site of metastasis is the lung. Of all possible organs, metastasis to the skeletal muscle is relatively unusual.* ***Case report:*** *A 22-year-old female diagnosed as malignant phyllodes tumor was referred and admitted to the department of surgery at our institute for further evaluation and management of the soft tissue masses found in the left forearm. Three years back, the patient underwent left sided mastectomy and subsequent chemotherapy for management of a malignant phyllodes tumor. Physical examination revealed a non-tender palpable mass on the left forearm. Histopathological examination revealed metastatic phyllodes tumor to the left forearm.* ***Discussion:*** *It has been estimated that breast cancer will account for the greatest number of newly diagnosed cancer and the second highest proportion of cancer related deaths among women.* ***Conclusion:*** *Most invasive primary breast cancers are epithelial derived adenocarcinoma, rare neoplasms such as the phyllodes tumor may arise from mesenchymal tissue.*

Keywords: *Phyllodes, malignant, metastasis*

Introduction:

Malignant Phyllodes tumors are relatively rare, accounting for 0.3% to 0.9% of all tumors of the breast. These tumors metastasizes approximately 20% of the cases depending upon the histologic behaviour. The most common site of metastasis is the lung. Of all possible organs, metastasis to the skeletal muscle is relatively unusual. Phyllodes tumor originally described in 1838 by Johannes Muller.[1, 2] Phyllodes tumor are rare fibroepithelial neoplasm which represents 0.3%-0.9% of all breast cancers and classically known as cystosarcoma phyllodes because of leaf-like projections.[3, 4] It was renamed phyllodes tumor in the early 1980.Classified into three categories: benign, borderline, malignant.[5] Majority of phyllodes tumors are benign.

Malignant phyllodes represent 10-30% of all phyllodes tumor.[6] Neoplastic stromal component may be monomorphic or highly pleomorphic and may be reminiscent of fibrosarcoma, MFH, liposarcoma, metaplastic cartilage, bone or skeletal muscle.

Case Report:

A 22-year-old female diagnosed as malignant phyllodes tumour was referred and admitted to the department of surgical oncology at NICRH for further evaluation and management of the soft tissue masses found in the left forearm [Fig 1, 2, 3 & 4]. Three years ago, the patient underwent left sided mastectomy [Fig 7 & 8] and subsequent chemotherapy for management of a malignant phyllodes tumour. She had lumpectomy and it was diagnosed as malignant phyllodes. Physical examination revealed a non-tender palpable soft tissue mass on the left forearm. Histopathological examination revealed metastatic malignant phyllodes tumour to the left forearm [Fig 5 & 6]. After three months of left sided amputation of upper limb she developed lung metastasis. She passed away after lung metastasis.

Fig-1: *Axillary soft tissue growth*

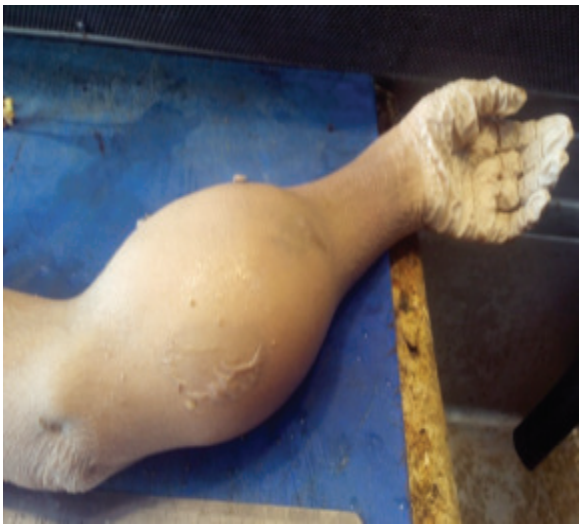


Fig-2: *Forearm soft tissue growth*

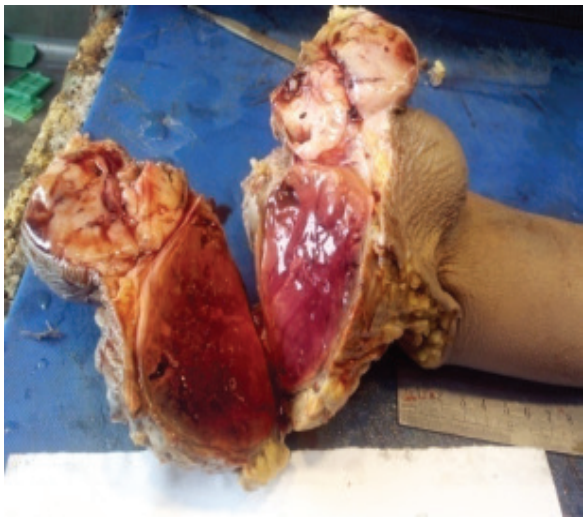


Fig-3: *Axillary soft tissue growth*

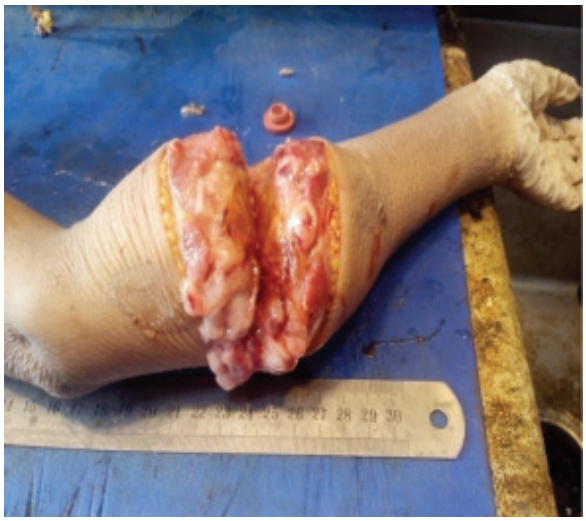
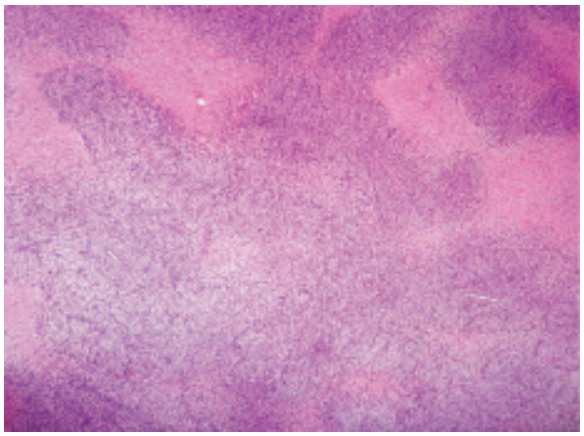


Fig-4: *Forearm soft tissue growth*



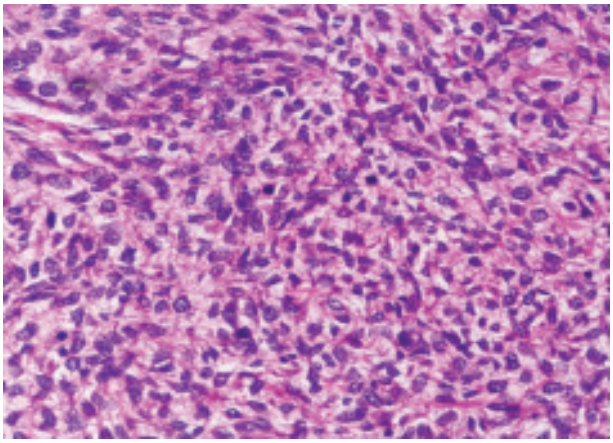
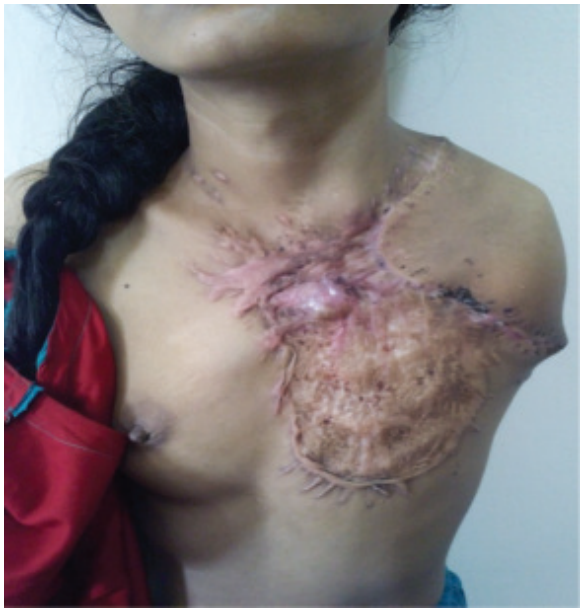


Fig-5&6: *Malignant spindle cells with atypical mitoses and areas of necrosis*



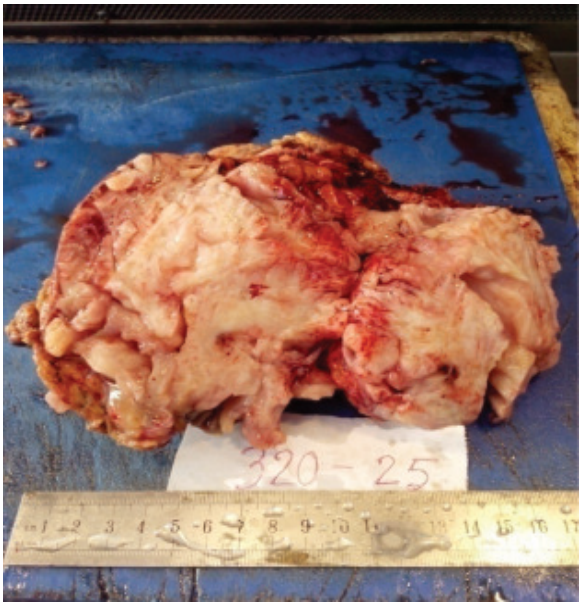


Fig-7&8: *Left sided mastectomy site and gross specimen of left breast*

Discussion:

Challenges facing physicians for patients with phyllodes tumour is predicting which patient will develop local recurrence, metastatic disease or both. The majority of the phyllodes tumors present as firm, smooth, well-circumscribed and rarely painful masses.[8] Most phyllodes tumor occur in women between ages of 35 and 55 years old. [9]

Primary treatment of phyllodes tumor is surgical. Depending on the size of the tumor, wide local excision is the treatment of choice. If margins of 1 cm cannot be attained, then simple mastectomy is the next best option. [10, 11]

In general, borderline tumors metastasize. In a case reviewed by Moffat et al. only 4% of patients with borderline tumors develop metastatic disease.[12] Malignant tumors develop metastasis more commonly. The overall metastatic rate of phyllodes tumor in general has been reported < 5%. [13]

According to WHOpredictors of malignant behavior are tumor size,cytological atypia, mitotic rate and stromal overgrowth. [14, 15] Some of the factors which have shown an increase in the change of local recurrence are tumour size, positive surgical margins, stromal overgrowth, high mitotic count and necrosis.

Geisler et al. had three patients which presented with metastatic disease to lung and thoracic vertebra who died 14 months after presentation. The other 2 patients presented with high grade MPT with metastatic disease-the first died 37 months following mastectomy with metastatic disease to the brain. The second patient was treated with partial mastectomy and died one month later with metastasis to the right sacral wing. [16]

Turalba et al. showed that doxorubicin and ifosamide-based chemotherapies have some efficacy in women with metastatic phyllodes tumour. Hormonal therapy is not effective in phlyllodes tumour despite the presence of positive hormone receptors. [17] Common site of distant metastasis are lungs, bone, liver, distant lymph nodes and brain.

Conclusion:

The phyllodes tumour is a rare mesenchymal primary breast cancer of middle-aged women. Exhibits rapid growth and shares many clinical, imaging and histopathological similarities with the benign fibroadenoma. A key to the successful management of this tumour may be early detection and resection prior to the development of distant metastasis.

Conflict of interest:

No financial disclosure.

Acknowledgement:

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Case Report

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A Young Man Presented with Prostatic Rhabdomyosarcoma: A Case Report

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Abstract

Background: *Prostatic rhabdomyosarcoma is malignancy of mesenchymal origin of prostate. It has an aggressive clinical course and predominantly disease of the children but rare in adult.* ***Case report:*** *An 18 years old boy presented with frequency of micturition for couple of weeks followed by acute retention of urine with severe abdominal and perineal pain. On digital rectal examination asymmetrically enlarged lobulated, non-tender prostate was revealed. His renal function was impaired (creatinine=2.3mg/DL). Transrectal biopsy reveals spindle cell with elongated, plum nuclei with brisk mitotic activity and necrosis suggestive of rhabdomyosarcoma which is confirmed by IHC. Chest X-ray and bone scan reveals no metastasis. The patient was given 2 cycle chemotherapy with ifosphamide and doxorubicin and his symptoms relieved and general conditions improved with relief from urinary tract obstruction and improvement of renal function.* ***Conclusion:*** *Prostatic rhabdomyosarcoma is a rare tumor and presents with a poor prognosis in adults. Latest imaging modalities may aid in the diagnosis and also help in an accurate staging of the disease, allowing a better therapeutic planning.*

Key words: *Rhabdomyosarcoma, prostate, adult*

Introduction:

Prostatic rhabdomyosarcoma is malignancy of mesenchymal origin of prostate.[1, 2] It has an aggressive clinical course and predominantly disease of the children.[3, 4] In adult it is rare and only around 30 cases have been described in English speaking literature.[4-6] Here we present such a case of rhabdomyosarcoma of the prostate and a review of the literature regarding the clinical features, diagnostic modalities and therapeutic aspects of this rare entity.

Case presentation

An 18 years old boy presented with frequency of micturition for couple of weeks followed by acute retention of urine with severe abdominal and perineal pain. He was evaluated and bladder was palpable, genitalia was normal and digital rectal examination reveals asymmetrically enlarged lobulated, non-tender prostate with variable consistency. His urine analysis with routine blood test including PSA(0.13ng/ml) was normal except his renal function was impaired (creatinine=2.3mg/DL) and ultrasound of abdomen shows a complex lobulated mixed echogenic mass of 14.2×8.2 cm diameter in the region of prostate and base of the bladder involving both ureteric sphincters with mild degree of bilateral hydronephrosis. Transrectal biopsy reveals spindle cell with elongated, plum nuclei

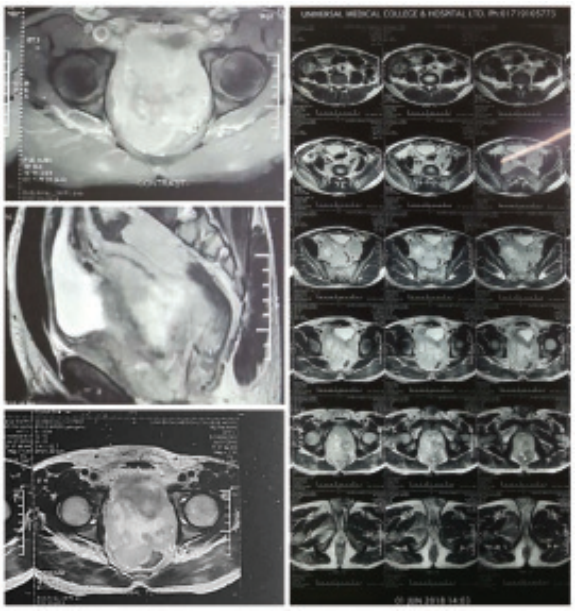

Fig.-1: *MRI of pelvis shows a lobulated heterogenous soft tissue mass from the prostate. Hypointense on T1 & hyperintense on T2 is observed. Mass invades the neck & base of the urinary bladder. Seminal vesicles and anterior wall of rectum are adherent and inseparable from the mass. Post contrast images revealed heterogenous enhancement of the mass. No ascites, lymphadenopathy or collection is noted.*

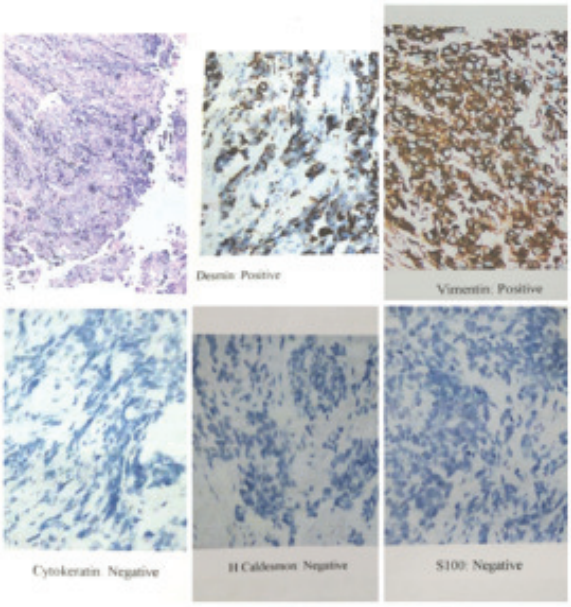

Fig-2: *Immunocytochemistry of paraffin block of enlarged prostate shows cytokeratin/Pankeratin-Negative, Vimentin-Positve, S-100-Negative, Desmin-Positive, H Caldosmin-Negative which is compatible with Rhabdomyosarcoma.*

with brisk mitotic activity and necrosis suggestive of rhabdomyosarcoma which is confirmed by IHC vimentin & desmin positive and h-caldesmon negative status. Further evaluation by MRI of pelvis reveals a lobulated heterogeneous mass of prostate involving the base of urinary bladder, seminal vesicle and ant wall of rectum with no pelvic & intra-abdominal lymphadenopathy. Chest X-ray and bone scan reveals no metastasis. With consultation with Medical oncology department patient received 2 cycle chemotherapy with ifosphamide and doxorubicin and his symptoms relieved and general conditions improved with relief from urinary tract obstruction and improvement of renal function.

Discussion

Mesenchymal origin prostatic malignancy of are rare, about 03% to 1.0% of all prostatic tumors. Almost thirty percent of these tumors are embryonal rhabdomyosarcoma. Children are primarily affected, and a very few cases in adults.Only about 10% of cases occur in adults and adenocarcinomas would be 3000 to 9000 times more common incident wise.[1]Usually leiomyosarcomas are the tumor of sarcomatous origin, occurring in a more advanced age range and with a better prognosis.[1,2,6,7] Generally, rhabdomyosarcoma are extremely aggressive, and present with distal metastasis at the time of diagnosis in 25% of cases.[4] Lungs are the single most common site, can also occur in bones, lymph nodes, liver and serosa.[1,3,8] Metastasis of bone are disseminated osteolytic, in contrary to adenocarcinomas that frequently occurs as osteoblasticmetastasis, commonly involving the axial skeleton.Displacement of bladder and rectum occurs as rhabdomyosarcoma locally invades periuretral, perivesical and perirectal tissues. Histologically, these tumors can be divided into embryonal,aggressive alveolar and a rare pleomorphic type mostly found in adult.[2,9] Almost 2/3rd of rhabdomyosarcoma are embryonal and can be sub divided into botryoid type, spinous cells and conventional type,with a superior prognosis in the first two cases.Lymphoma and small cell carcinoma are the justified differentials excluded by immuno-histochemistry. Obstructive urinary symptoms resulting from a significant increase in the prostatic volume are usual presentation.

Hematuria,incontinence and pelvic pain is a frequent finding, and usually requires strong analgesia. Compression or invasion of perirectal planes compression or invasion results in obstructive intestinal features.[1,3,4,8] Imaging studies are not common, and no specific pattern that is confirmed by Ultrasound-guided transrectal biopsy.[4,7] Presence of a large mass on the prostatic bed, infiltrating adjacent planes in a young patient with normal prostatespecific antigen (PSA) may be a clue to diagnosis. Ultrasound finding commonly hyper or hypo-echogenic, with lucent areas corresponding to hemorrhage or necrosis sites.

We could not find any previous report on doppler velocimetric profile characteristic of the lesion. Reports describe hyperemia and high diastolic flow velocity in para-testicular rhabdomyosarcoma of children.[3] In the case presently described, US has also allowed the diagnosis of the tumor extension to the left seminal vesicle, proved by pathological study.CT demonstrates an infiltrative, manytimes ill-defined mass with heterogeneous attenuation, whose prostatic of vesicle site of origin cannot be identified.[10] At MRI, the primary tumor shows nonspecific low signal intensity on T1-weightedsequences, and high signal intensity on T2-weighted sequences. Heterogeneous signal intensity representing hemorrhagic foci may be identified. MRI allows a more accurate evaluation of the local tumor extent and involvement of adjacent planes as compared with US and CT. [3,5,11] This could be observed in the present study.The utilization of PET/CT for rhabdomyosarcoma staging in adult individuals is still to be consolidated in the literature, however, reports on cases involving children have demonstrated the relevance of this method in the detection of the primary focus in metastatic disease, obscure metastases and in unusual sites.[12] In the present case, PET/CT was extremely useful in the detection of distant lymph node metastases.The treatment of this disease is performed with chemotherapy in association,or not, with surgical resection and/or radiation therapy. The prognosis is poor, with a five-year survival rate of 30%-35% for all rhabdomyosarcoma in adult individuals.[6,13] This rate is probably lower in cases of primary tumor on the prostatic bed.

Conclusion

Prostatic rhabdomyosarcoma is a rare tumor with more aggressive potential and presents with a poorer prognosis in adults as compared with its presentation in children. New horizon of imaging diagnosis may aid in the diagnosis and also help in an accurate staging of the disease, allowing a better therapeutic planning.

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Review Article

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A Review Analysis of Reirradiation for Recurrence Rectal Cancer: Feasibility, Toxicity and Outcome

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Abstract:

Local recurrence of rectal cancer is infrequent, reirradiation may be needed to improve resectability and outcomes. This current review explored the effects of reirradiation in context of feasibility, acute and late toxicity, and long-term outcomes. A search resulted in 63full texts/abstracts. Eight publications describing prospective or retrospective studies were included, presenting results of 409 patients reirradiated for rectal cancer. Median initial radiation dose was 50.4 Gy, median time interval was 8–30 months since reirradiation. Reirradiation was mostly given using hyperfractionated (1.2–1.5 Gy twice a day) or 1.8 Gy once-daily chemoradiotherapy. Median total dose was reported to be 30–40 Gy to the gross tumour volume with 2–4 cm margins. In resected patients, median survival was 39–60 months and in palliative patients, it was 12–16 months. Favourable symptomatic relief was reported in 82–100%. Acute toxicity with diarrhoea was reported in 9–20%, late toxicity was less reported. Reirradiation of rectal cancer to limited volumes is an open option. When curative surgery is feasible one should go for radical resection to achieve long-term survival, Hyperfractionated chemoradiotherapy should be preferred to limit late toxicity. Reirradiation yielded favourable symptomatic relief in palliative treatment.

Key wards: *Reirradiation, Recurrence, Rectal cancer, Survival, Palliative treatment.*

Introduction:

Rectal cancer is a common disease world-wide with an age-standardized incidence rate of 17.3 per 100,000 person-years.[1] Appropriate surgery with total mesorectal excision[2] and increased use of preoperative radiotherapy (RT) and chemoradiotherapy (CRT) have helped to decrease recurrence rates.[3] Population-based studies in different regions have confirmed increased survival of patients with rectal cancer.[4] Local recurrence of rectal cancer can be a distressing condition, because of intractable pain, pelvic infection, and obstruction, which hampers quality of life (QOL).[5] An increasing

proportion of patients with local recurrence have previously received high-dose pelvic radiotherapy as part of their treatment, either as preoperative short-course radiotherapy (5 x 5 Gy) or as chemoradiotherapy to 45–50 Gy (1.8–2.0 Gy/fraction). Curative resection of the local recurrence is the most important factor for increase survival.[6] Reirradiation of previously irradiated patients may increase the rate of radical resection (R0) and may also provide palliation of symptoms for inoperable cases.[7] It is therefore vital to determine the safety and benefits of reirradiation in patients with local recurrence. To optimize the radiotherapy, the tumour should receive a high total dose while sparing the surrounding normal tissue to avoid toxicity. Reirradiation is critical, because the surrounding normal tissues may have already received doses near the organ- or endpoint-specific tolerance dose during the previous treatment. Reliable clinical data on long-term normal tissue recovery and radiation tolerance doses are rare. However, there is increasing evidence in clinical studies that reirradiation is tolerable and yields good results for different tumour locations.[8] The potential tissue injury caused by retreatment should be weighed against the expected benefits in terms of achieving R0 surgery and long-term survival. If potentially curative treatment is predicted, the treatment planning with conformal doses should be planned, and hyperfractionation should be considered for radiobiological reasons to reduce the risk of late effects.[9]

The aim of the current review was to explore and evaluate the efficacy and safety reported in different published papers in the context of the feasibility, outcomes, and toxicity of reirradiation of previously irradiated locally recurrent rectal cancer patients. The main focus was on external beam reirradiation, all fractionation regimens, with or without concurrent chemotherapy; reirradiation combined with other radiotherapy modalities are only briefly discussed.

Methods:

A search strategy included terms such as (anorectal or rectal or rectum) and (neoplasms or cancer or tumour) and (reirradiation), with no limitations for year of publication and full-text/abstract copies of all potentially relevant studies were obtained. Published full-text/abstract studies that evaluated reirradiation of rectal, anorectal or rectosigmoid cancer were considered for inclusion. Studies of patients with locally recurrent rectal cancer were eligible if they included patients previously irradiated for rectal cancer and if they reported outcomes after additional external beam radiotherapy with or without concomitant chemotherapy. Prospective, retrospective, and randomized controlled trials were eligible. Case reports and reviews were excluded. Studies evaluating external beam reirradiation combined with other radiation techniques such as Brachytherapy or intraoperative radiotherapy (IORT) were not included. Data regarding patient characteristics, previous radiotherapy, reirradiation details, and outcomes were extracted from the studies independently and presented in tables. A meta-analysis was not feasible due to heterogeneity of studies and outcomes. For patients treated with curative intent, the effects of reirradiation in terms of R0 resection rate, survival, and acute and late toxicity were evaluated. For patients treated with palliative intent, the effects of reirradiation on symptom palliation, survival, toxicity, and QOL were evaluated. The clinical implications of reirradiation in terms of total dose, target volume, and fractionation regimens, and possible recommendations for clinical practice, were discussed.

Results:

The search resulted in 404 titles/abstracts were screened, and 63 full-text publications were reviewed. Eight studies met the inclusion criteria and were included in the final analysis.[10-17]There were no randomized controlled studies; all studies were prospective or retrospective (Table 1). A total of 409 patients treated with reirradiation (range 22–103) were included. The median age ranged from 50 to 69 years, and the proportion of male patients was 52–78%. The median previous RT dose was mostly 50.4 Gy, previous fractionation regimen was rarely described, but assumed to be 1.8–2.0 Gy per fraction. The median time since previous RT varied from 25 to 40.3 months. Reirradiation doses and techniques are summarized in Table 2. The median reirradiation dose given was 30.6–36 Gy, delivered by opposed lateral fields or three-field technique, encompassing the presacral region and gross tumour volume (GTV) with 2–4 cm margins, and combined to concomitant 5-fluorouracil (5-FU) continuous infusion. Patients with recurrent rectal cancer1.2 Gy twice daily with concomitant5-FU was given to the GTV plus a 4-cm margin to a total dose of30 Gy; thereafter, additional CRT to a total of 40.8

Table 1: Study characteristics, patient characteristics, and details of previous radiotherapy

Author & publication year	Study design and inclusion period	Re-irradiated N	Patient population	Median age years (range)	Previous RT dose median, Gy (range)	Time since RT median, months (range)
Park 2019	Retrospective 2005-20115	25	ARC, previous pelvic RT	50 (31-75)	50.4 (50.4-59.4)	40.3 (11.7-218.5)
Cai 2014	Prospective 2007-2012	22	RC, previous pelvic RT	53 (40-68)	48.6 (36-62)	30 (18-93)
Ng 2013	Retrospective 1997–2008	56	RC, previous pelvic RT Curative n = 13, Palliative n = 43	69 (26–88)	50.4 Gy (21–64)	30 (8–176)
Sun 2012	Prospective 2004–2008	72	Recurrent irresectable RC	59 (29–78)	<50 Gy (NR)	25 (13–77)
Koom 2012	Retrospective 2000–2007 22	22	Recurrent RC	50 (33–64)	54 Gy (45–59.4)	26 (5–72)
Das 2010	Retrospective 2001–2005	50	RC, previous pelvic RT Primary n = 2, Recurrent n = 48	60 (32–80)	47 Gy (25–70)	28 (5–354)
Valentini 2006	Prospective phase II 1997–2001	59	Recurrent RC No extra-pelvic disease	62 (43–77)	50.4 Gy (30–55)	27 (9–106)
Mohiuddin 2002	NRa 1987–2000	103	Recurrent RC	65 (31–79)	50.4 Gy (30–74)	19 (2–86)

NR = not reported in original publication; ARC= anorectal cancer; RC = rectal cancer; RT = radiotherapy.

Table 2: Reirradiaton treatment

Author & year	Planned RT Per-fraction dose/ total dose	Re-RT median (range)	Treatment volume	Technique	Cumulative dose median (range)	CCT
Park 2019	2 Gy/ NR	45 (36–60)	Tumour bed + 5-10 mm	3DCRT/ IMRT/ both	92.5 (80.1–199.8)	Yes n=14
Cai 2014	1.3 Gy bid/ 39 Gy	39 Gy	GTV PTV= GTV + 2-3 cm	IMRT 5 fields	NR	No
Ng 2013	1.8 Gy/39.6 Gy	39.6 Gy (20–39.6)	GTV CTV = GTV + 1 cm PTV = CTV + 1 cm	3DCRT 2–4 fields or IMRT	87.3 Gy (44.4–108)	5-FU
Sun 2012	1.2 Gy bid/30–36 Gy (n = 18) Non-resectable: redraw GTV, total 51.6–56.4 Gy (n = 54)	-	GTV CTV = GTV + 1 cm PTV = CTV + 1 cm	3DCRT 5–8 fields	NR	Capcitabine
Koom 2012	1.8–3 Gy/NR	50.2 Gy (30–66)	GTV + 2–3 cm	3DCRT or IMRT or Tomotherapy	103.3 Gy (81–119.4)	Yes
Das 2010	1.5 Gy bid/30–39 Gy	39 Gy (94%) 30 Gy (6%)	GTV + 2–3 cm	3-field	NR	Capcitabine
Valentini 2006	1.2 Gy bid/30 Gy (PTV2) +1.2 Gy bid/10.8 Gy (PTV1)	40.8 Gy	GTV + 4 cm (PTV2) GTV + 2 cm (PTV1)	3DCRT	NR	5-FU
Mohiuddin 2002	1.2 Gy bid/30 Gy + boost6–20 Gyb (n = 43)or 1.8 Gy/30.6 Gy + boost 6–20 Gy (n = 60)	34.8 Gy (15–49.2)	Presacral region and GTV + 2–4 cm, Boost: GTV + 2 cm	2 lateral fields or 3-field	85.8 Gy (70.6–108)	5-FU

CCT: concurrent chemotherapy; Bid: two fractions daily; GTV: gross tumour volume; CTV: clinical target volume; PTV: planning target volume; 3-field: 1 posterior and 2 lateral fields.3DCRT: 3-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy; 5-FU: 5-fluorouracil; NR: not reported.

Gy was given to GTV plus 2-cm margin.[16]Patientswho received 1.5 Gy twice daily and concomitant 5-FUwith a long interval since previous treatment (P1 year) received a total dose of 39 Gy, and patients with shorter intervals 30 Gy.[15] The treatment was delivered to GTV with a 2–3 cm margin, mostly by three-field technique. A smaller series of patients treated more heterogeneously with 1.8–3.0 Gy once daily, to a median reirradiation dose of 50.2 Gy, with techniques including conformal RT, intensity-modulated radiation therapy (IMRT), and tomotherapy.[14]Patients treated with 1.2 Gy twice daily to a reirradiation dose of 30–36 Gy delivered by 5–8 fields delivered to GTV plus 2 cm, with concomitant capecitabine.[13] In non-resectable patients, the GTV was redrawn and RT continued to a total dose of 51.6–56.4 Gy, thus delivering a high reirradiation dose to patients with irresectable local recurrence. Finally, patients with rectal cancer who had had previous pelvic radiotherapy, of whom 40% had metastatic disease. They were treated with 1.8 Gy once daily to a reirradiation dose of 39.6 Gy, with concomitant 5-FU. The treatment volume included GTV plus a 2-cm margin; most patients were treated by three-field technique and some with IMRT.[10]

To summarize the treatment given, reirradiation for rectal cancer was mostly given with hyperfractionated chemoradiotherapy to total doses of 30–40 Gy, although higher doses have been explored. Once-daily reirradiation was mostly used for palliative intent. The treatment volumes encompassed the tumour with margins, in newer studies delivered by multiple fields. The median follow-up time ranged from 15 to 36 months (Table 3). R0 resection was obtained in 39–89% of patients who underwent tumour resection; the wide range probably reflecting differences in patient selection. Further local recurrence occurred in approximately 50% of resected patients. The median survival ranged from 39 to 60 months in resected patients and from 12 to16 months in palliative patients. A high proportion of patients reirradiated with palliative intent to median doses of e”30 Gy obtained symptomatic relief (Table 3) The proportion with complete or partial pain relief ranged from 83% to 94%. Rectal bleeding resolved completely in 100% of patients. The majority (>80%) of patients experienced partial or complete symptom relief from gastrointestinal symptoms or rectal mass. The median duration of symptom relief was 8 months for mass effect, 9 months for pain, and 10 months for bleeding.[17]

Table 3: *Treatment results after reirradiation*

Author & year	Follow-up median, months (range)	Surgery tumour resection, n (%)	Survival median, months			Symptom palliation, n (%)
			All	Resected	Palliative	
Park 2019	22 (3 - 84)	Surgery 11/25 (44%)	-	41	5	Overall (CR+PR) 9/10 (90%)
Cai 2014	17 (2-59)	No	19	-	-	Overall CR 6 (27%), PR 13 (59%) Overall RR 88%, CR 24/49 (49%), PR 19/49 (39%)
Ng 2013	15 (1–108)	Surgery 12/56 (21%) Resection 11/56 (20%) R0: 8	19	39	15	Rectal bleeding/discharge 100% GI CR 50%, PR 50% Pain CR 47%, PR 44% Urinary CR 1/1 (100%) Vaginal bleeding CR 2/3 (67 %)
Sun 2012	24 (10–57)	Resection 18/72 (25%) R0: 16	32	-	-	Pain relief 29/31 (94%) Tenesmus relief 23/28 (82%)
Koom 2012	20 (7–91)	Resection 5/22 (23%)	21	-	-	-
Das 2010	25 (0–71)	Resection 18/50 (36%) R0: 7	26	60	16	-
Valentini 2006	36 (9–69)	Resection 30/59 (51%) R0: 21	42	-	-	Pain relief 20/24 (83%)
Mohiuddin 2002	24 (3–84)	Surgery 41/103 (40%) Resection 34/103 (33%)	26	44	14	Bleeding CR 21/21 (100%) Pain CR 25/46 (54%), PR 13/46 (28%) Mass effect CR 9/36 (25%), PR 23/36 (64%)

Radical surgery and survival after reirradiation. Symptom palliation in non-resected patients.
R0: number of patients with microscopic radical resection; RR: response rate; CR: complete response; PR: partial response.

Table 4: *Acute and late toxicity after reirradiation*

Author & year	Planned RT Per-fraction dose/ total dose	Re-RT median (range)	Treatment volume	Technique	Cumulative dose median (range)	CCT
Park 2019	2 Gy/ NR	45 (36–60)	Tumour bed + 5-10 mm	3DCRT/ IMRT/ both	92.5 (80.1–199.8)	Yes n=14
Cai 2014	1.3 Gy bid/ 39 Gy	39 Gy	GTV PTV= GTV + 2-3 cm	IMRT 5 fields	NR	No
Ng 2013	1.8 Gy/39.6 Gy	39.6 Gy (20–39.6)	GTV CTV = GTV + 1 cm PTV = CTV + 1 cm	3DCRT 2–4 fields or IMRT	87.3 Gy (44.4–108)	5-FU
Sun 2012	1.2 Gy bid/30–36 Gy (n = 18) Non-resectable: redraw GTV, total 51.6–56.4 Gy (n = 54)	-	GTV CTV = GTV + 1 cm PTV = CTV + 1 cm	3DCRT 5–8 fields	NR	Capcitabine
Koom 2012	1.8–3 Gy/NR	50.2 Gy (30–66)	GTV + 2–3 cm	3DCRT or IMRT or Tomotherapy	103.3 Gy (81–119.4)	Yes
Das 2010	1.5 Gy bid/30–39 Gy	39 Gy (94%) 30 Gy (6%)	GTV + 2–3 cm	3-field	NR	Capcitabine
Valentini 2006	1.2 Gy bid/30 Gy (PTV2) +1.2 Gy bid/10.8 Gy (PTV1)	40.8 Gy	GTV + 4 cm (PTV2) GTV + 2 cm (PTV1)	3DCRT	NR	5-FU
Mohiuddin 2002	1.2 Gy bid/30 Gy + boost6–20 Gyb (n = 43)or 1.8 Gy/30.6 Gy + boost 6–20 Gy (n = 60)	34.8 Gy (15–49.2)	Presacral region and GTV + 2–4 cm, Boost: GTV + 2 cm	2 lateral fields or 3-field	85.8 Gy (70.6–108)	5-FU

CCT: concurrent chemotherapy; Bid: two fractions daily; GTV: gross tumour volume; CTV: clinical target volume; PTV: planning target volume; 3-field: 1 posterior and 2 lateral fields.3DCRT: 3-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy; 5-FU: 5-fluorouracil; NR: not reported.

The rate of treatment interruption or termination due to toxicity was>30% in the earlier studies (Table 4)[17] and was later reduced to 13%, 5%and 4%.[10-16] This reduction in acute toxicity seems to be correlated with increasingly conformal radiotherapy and smaller margins to the GTV, and possibly better selection. The most commonly observed grade3–4 toxicities were diarrhoea and skin reactions (Table 4), the frequency reduced in the later studies. Late toxicity was not prospectively evaluated probably because most studies were retrospective, follow-up was relatively short, and patients treated with palliative intent had limited life expectancy. The most commonly reported late toxicities were gastrointestinal and urinary complications such as small bowel obstruction, fistula, stricture, chronic diarrhoea, and cystitis (Table 4). Factors that influenced the development of late toxicity included surgery, prior radiotherapy dose, interval between initial radiotherapy and reirradiation, tumour location within the pelvis, and fractionation regimen.[10-17] None of the studies evaluated health-related QOL.

Discussion:

This review of reirradiation for locally recurrent rectal cancer patients revealed that reirradiation is possible and has acceptable acute toxicity, although data on late toxicity is scarce. Reirradiation was delivered as hyperfractionated or once-daily regimens to total doses of 30–40 Gy to the GTV with 2–4 cm margins along with concurrent chemotherapy. The aims of the treatment were to achieve a curative resection with radical surgery, or to attain tumour control and symptom palliation. It is widely reported that radical surgery is the main predictor for getting survival benefits.[6,18] Thus, an aggressive multimodal and surgical approach is justified if R0 resection is feasible. Surgery of local recurrence is difficult, as the normal anatomical boundaries are no

longer retained and previous radiotherapy might have caused fibrosis, and other pelvic organs or structures might have involved with recurrence.[18] Reirradiation might help to down size the tumour and increase the chance of an R0 resection[17], though it is not clear whether all patients get benefits from reirradiation. Patients with surgical intervention experienced a longer median survival than patients with inoperable disease.[12,14,15,17] however toxicity was more reported in patients who underwent surgery.[12,13] It was difficult to understand whether late toxicity was due to surgery, radiotherapy or from complexity of further recurrence.

The distinction between curative and palliative intent is usually not clear. As per several studies it was depended on whether patients were eligible for curative surgery after reirradiation. Patients reirradiated with palliative intent had a shorter life span, but reported favourable symptom palliation of bleeding, pain, and gastrointestinal symptoms.[12,13,17] This is in line with another review of palliative radiotherapy for rectal cancer, reporting good symptomatic relief[19], and a review reporting efficacy of reirradiation for bone metastases.[20] The need for palliation of symptoms the expected outcome of reirradiation must be weighed against the expected survival benefits. It is worth noting that the small bowel and the bladder are main organs at risk. However, clinical evidence regarding reirradiation tolerance is not available[21], and dose constraints are not provided. For small bowel, there are suggestions for constraints in the literature to minimize acute toxicity[22], and experimental data suggests consequential chronic damage; however, a correlation with late toxicity has not been established yet. For bladder, experimental studies suggest no late toxicity recovery, and a strong consequential component[9], but reliable tolerance data are not known. Surgery in reirradiated patients is often extensive and may result in colostomy and urostomy. Complications like bleeding, obstruction, perforation, incontinence and fistula are also associated with persistent or recurrent disease.[14,17] Reirradiation should be practiced in limited volumes using small margins thereby reducing small bowel and bladder doses. [9,22]

Most studies reviewed in this paper used hyperfractionated radiotherapy, administered in 1.2–1.5 Gy fractions twice a day, at least for curative treatment.[11,12,17] Once-daily fractions (1.8 Gy) were mostly a palliative treatment option or patient preference.[10,13,18] The fractionation regimens were believed to be chosen on radiobiological rationale, extrapolation from other tumour sites, and feasibility. Several studies used different regimens but patients were not randomized which made comparison between schedules very difficult. The basis for hyperfractionated, accelerated therapy is that small fraction doses increase the therapeutic ratio by exploiting the difference in fractionation sensitivity between tumour (highá/â) and late-reacting normal tissue (low á/â).[23] Reirradiation doses can be recalculated to equivalent doses delivered with 2 Gy fractions (EQD2Gy) for comparison of fractionation schemes (EQD2Gy = n * d * ((d + á/â)/(2 + á/â)). A total dose of 39.6 Gy delivered with 1.2 Gy/fraction gives EQD2Gy = 33.3 Gy for late-reacting tissue (á/â = 3 Gy), and a higher EQD2Gy = 37.0 Gy for tumour (á/â = 10 Gy), assuming adequate time between the fractions to allow normal tissue recovery. Repair half-times for human small bowel are not certain, but assuming an incomplete repair factor of 0.063 based on animal models[9], normal tissue has full recovery by 6 h. Hyperfractionated reirradiation should be the preferred treatment option for curative intent. It may also be given in patients with inoperable tumour with a relatively long-life expectancy, with the aim of durable local control. Although some patients with metastatic disease have long survival with combination chemotherapy, many patients with disseminated disease or poor performance status have a short life expectancy, and the risk of late effects is less relevant. For these patients, once-daily reirradiation has been shown to be feasible as well as effective.[7,12] Although, treatment techniques have become more sophisticated with time, the treatment principles remained the same. In earlier studies, computed tomography (CT) was probably not used for treatment planning; the target volume was the gross tumour with margins of 2–4 cm and the presacral space, given by opposed lateral fields to spare the anteriorly situated small bowel.[17] In recent studies, the GTV was delineated and margins of 1 cm to the clinical target volume (CTV) and 1 cm to the planning target volume (PTV) were added.[10-14]Treatment was delivered by conformal radiotherapy or IMRT[10-12,14] to ensure high tumour doses with tolerable small intestine and bladder doses. There was a trend towards less acute and late toxicity in the recent studies, probably due to better conformal treatment. The total dose administered was

mostly at the level of 30–40 Gy; however, some studies administered a higher dose to a smaller volume, depending on time passed since previous radiotherapy[17] or in inoperable patients.[12] One study showed that reirradiation doses >50 Gy increased the infield progression-free survival.[13] For patients with inoperable disease, it seems that higher doses can be administered safely, especially with conformal CRT or IMRT, provided sufficiently low normal tissue doses. In one study, escalated doses of 51.6–56.4 Gy with 5–8 fields were administered, with dose limitation to the bladder of 30 Gy and to the small intestine10 Gy for <50% of volume.[12] A short time interval since previous radiotherapy may result in worse radiation tolerance.[13,17] Modern imaging (i.e., MRI and positron emission tomography) and radiotherapy techniques (e.g., conformal RT and IMRT) allow more precise target delineation, accurate dose distribution, and narrow margins. Future trials should aim at prospective assessment of tumour and normal tissue doses, investigate the optimal fractionation regimen, as well as acute and late toxicity including patient-reported outcomes and QOL. Central review of CTV delineation in rectal cancer may increase the CTV uniformity, and can be used for quality assurance for radiation treatment.[24,25]Although treatment of previously irradiated patients with recurrent rectal cancer might pose challenges, several studies have shown that reirradiation is possible, safe, and effective in terms of achieving radical resection or palliation.

Conclusion:

Retreatment is believed to be safer with modern staging and radiotherapy techniques. Patients should undergo adequate diagnosis and have easy access to tumour board in experienced centers, and ideally be included in prospective trials. If the intent is only palliative and expectancy of life is short, once daily chemo-radiotherapy is probably the best treatment option for the patients.

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