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Editorial

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Cancer and Palliative Care

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World Hospice and Palliative care day is celebrated worldwide on the second Saturday of October. Let us define the term *palliative care* and *hospice* first. Palliative care is holistic care that relieves symptoms of a disease or disorder, whether or not it can be cured. Palliative care encompasses the patient and involves improving the quality of life of the caregivers concerned. Hospice is a specific type of palliative care for people who have few months or less to live. Due to various factors, the burden of non-communicable diseases (NCDs) is increasing globally. So, the need for palliative management is also increasing. According to WHO statistics, an estimated 56.8 million people each year, including 25.7 million in the last year of life, require palliative care. Nevertheless, the sad part of the picture is that only about 14% of people who need palliative care currently receive it. In Bangladesh, the actual scenario is not precise due to a lack of appropriate data.[1]

Palliative care is required for various diseases. The majority of patients who require palliative care have chronic diseases such as cardiovascular diseases (38.5%), cancer (34%), COPD (10.3%), AIDS (5.7%), and diabetes (4.6%). Some other conditions may require palliative care, including kidney failure, chronic liver disease, multiple sclerosis, rheumatoid arthritis, neurological disease, Parkinson's disease, dementia, congenital anomalies, and drug-resistant tuberculosis.[2]

Unlike other NCDs, cancer management and palliative care cannot be separated. In fact, for cancer, the need for palliation starts from the day of the first diagnosis. Often cancer patients experience intense pain, and prompt and effective pain management is as important as the treatment of cancer itself.

The mortality rate from cancer is usually very high. The reality is that some people do die from cancer. As people draw closer to death, the end-of-life aspect of palliative care becomes essential. Palliative care focuses on the symptoms and stress of the disease and the treatment. It treats pain, depression, anxiety, fatigue, shortness of breath, constipation, nausea, loss of appetite, & difficulty sleeping.

The scope of getting palliative care in our country is limited. However, the good thing is that the context is slowly changing. The official is now recognizing the need to extend palliative care to the whole country. Recently, a 10 bedded comprehensive palliative care ward was inaugurated at the National Institute of Cancer Research and Hospital. A dedicated trained team led by an Associate Professor is involved in providing all sorts of palliative care upon referral from different departments. The outpatient activity of the palliative care department is already running successfully.

There are some challenges also. First, awareness regarding palliative care among care receivers and caregivers is scarce. Second, unnecessarily restrictive regulations for morphine and other essential controlled palliative medicines deny access to adequate palliative care. The International Narcotics Control Board found that in 2018, 79% of the world's population, mainly people in low- and middle-income countries, consumed only 13% of the total amount of morphine used for the management of pain and suffering, or 1% of the 388 tons of morphine manufactured worldwide.[3]

Third, updated national policies, programmes, resources, and training on palliative care among health professionals are urgently needed to improve access.

WHO's response to promote palliative care is crucial. Indeed, palliative care medicines, including morphine, are included in WHO Essential Medicines List and the WHO Essential Medicines List for Children.[4]

The need for palliative care will continue to grow due to the aging of populations and the rising burden of non-communicable diseases and some communicable diseases. Early delivery of palliative care reduces unnecessary hospital admissions and health services. To cope with the new challenges, physicians, nurses, support workers, paramedics, pharmacists, physiotherapists, and volunteers should be prepared.

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Original Article

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Formalin Therapy in Radiation Proctitis

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Abstract

Background: *Chronic radiation-induced proctitis leads to recurrent or massive hemorrhage, necessitating hospitalization and requiring repeated blood transfusions. Formalin therapy is an effective treatment method for radiation proctitis with no significant complications.* ***Objectives:*** *This study aimed to see improvement of bleeding per rectum caused by radiation proctitis by formalin application and to evaluate any complication of this treatment.* ***Methods:*** *We did a prospective analysis of 10 patients suffering from bleeding per rectum following pelvic radiotherapy. We did this study in two centers. 1) National Institute of Cancer Research and Hospital, Dhaka. 2) Laser Colorectal Center, Dhaka. The study period was from January 2019 to December 2021. Patients experiencing bleeding per rectum following pelvic radiotherapy after failed medical treatment were included in the study.* ***Results:*** *This prospective study involved 10 patients. All of these patients were previously treated conservatively for haemorrhage and, as no improvement occurred, were referred for formalin therapy. Complete improvement of bleeding in 4 patients, partial improvement in five patients, and one patient had no improvement and later required a diversion colostomy.* ***Conclusion:*** *In our study, we found 4% formalin application to be safe, moderately effective, and a cheap alternative, with no signification complications in treating radiation-induced haemorrhagic proctitis.*

Keywords: *Formalin therapy, Radiation proctitis, Cervical cancer, External Beam Radiotherapy*

Introduction:

Radiotherapy is an essential treatment modality for pelvic malignancies such as gynecological, rectal, and prostate cancer. The use of radical doses of radiation in Gynaecological and prostate cancer leads to a significant proportion of patients being cured. However, such high doses also cause the development of significant late toxicities among long-term survivors.[1]

Chronic radiation proctopathy (CRP) is one of the most bothersome late toxicities among patients treated with radical pelvic RT. Incidence is reported to be as high as 20%. CRP could occur either as a continuation of acute symptoms three months after the completion of RT or symptoms that begin three months after the initiation of RT. The median onset is 8–12 months, but onset can occur as late as 30 years.[2] Common symptoms include diarrhoea, tenesmus, mucus/blood per rectum, urgency, incontinence, and pain. The complaint of most concern would be rectal bleeding.[3]

Refractory hemorrhagic CRP is difficult to manage, but previous successful experience in treating cystitis has

led to the use of formalin as a treatment option.[4] Topical formalin application has been extensively studied, and most results show that it is a simple, safe and effective way to treat hemorrhagic CRP. Formalin can be applied by direct instillation or endoscopy-guided placement of formalin-soaked gauze.[4] Formalin acts only on the superficial mucosa, which results in rapid deterioration of mucosal blood flow and superficial coagulation necrosis.[5]

Chronic radiation-induced proctitis leads to recurrent or massive hemorrhage, necessitating hospitalization and requiring repeated blood transfusions.[6] Common medical therapy for radiation-induced rectal proctitis includes non-steroidal anti-inflammatory agents (such as oral or topical sulfasalazine, acetylsalicylic acid and ibuprofen), oral corticosteroids, rectal steroid retention enema, sucralfate enemas, and bile-acid sequestering resins and, short chain fatty acid enemas. However, these drugs are not sufficiently effective and have limited benefits.[9, 10] Surgical excision of the rectum is difficult and may be associated with significant morbidity and even mortality due to advanced primary disease, adhesions, and the poor healing of irradiated tissue. Surgery is only performed in the presence of necrosis, perforation, stricture, or life-threatening hemorrhage.[7] Endoscopic therapy with various devices (bipolar cautery, YAG laser, argon laser, heater probes, and, more recently, argon plasma coagulation) has been reported to be effective in managing radiation-induced bleeding management.[6,11-13]

Formalin treatment has also been studied and most of the data suggest that it is an effective method of treating radiation induced hemorrhagic proctitis. No significant local or systemic toxic effects were observed following rectal instillation of 4% formalin. Its mechanism of action is likely to be local chemical cauterization of telengiectatic mucosal vessels.[6,10] Here we present our experience in 10 patients whose hemorrhagic radiation proctitis were treated with 4% endoluminal formalin application.

Materials and methods:

We did a prospective analysis of 10 patients who have been suffering from bleeding per rectum following pelvic radiotherapy. We did this study in 2 centers. 1. National institute of cancer research and hospital, Dhaka. 2. Laser colorectal center, Dhaka. Study period was from January, 2019 to December, 2021.

Inclusion criteria:

1. Bleeding per rectum following pelvic radiotherapy after failed medical treatment.
2. Rectum is free of malignancy.

Exclusion criteria:

1. Patients with large ulcers, mucosal necrosis, or stricture due to increased risk of perforation;
2. Patients with relapse of a primary tumor.

Variables:

Demographic variables:

1. Age
2. Sex

Clinical variables:

1. Primary neoplasm.
2. Type of radiotherapy.
3. Onset of bleeding after radiotherapy.
4. Frequency of blood transfusions.
5. No of formalin application sessions.
6. Complications after formalin therapy.
7. Improvement after formalin therapy.

Procedure:

All patients received colonoscopic evaluation before formalin irrigation. Complete bowel preparation given to all patients with Polyethylene glycol. Patients gave IV sedation with propofol and kept in left lateral position. 150 ml 4% Formalin given with colonoscope to the involved area of rectum. Air is sucked with colonoscope and then the scope is retrieved. Formalin kept for three minutes. Then suction of Formalin done with scope. Perineal wash done with normal saline. Patients can go home after one hour. Repeated Formalin therapy can be done after one month if less improvement of bleeding per rectum.

Follow up:

Follow up done 1 week, 1 month and 6 months after Formalin therapy.

Results

Table I:

Serial	Age (years)	Sex	Primary neoplasm	Type of radiotherapy	Onset of bleeding after radiotherapy (months)	Frequency of blood transfusion (unit)
1	50	F	Cervical cancer	External beam	6	0
2	55	F	Cervical cancer	External beam	6	5
3	52	F	Cervical cancer	Brachytherapy	1/2	4
4	55	F	Cervical cancer	External beam	6	10
5	50	F	Cervical cancer	External beam	8	6
6	72	F	Cervical cancer	Brachytherapy	24	4
7	55	F	Cervical cancer	External beam	24	6
8	45	F	Ovarian cancer	External beam	3	10
9	33	F	cervical cancer	brachytherapy	6	4
10	42	F	Cervical cancer	External beam	3	20

Table II:

Serial	No of Formalin application sessions	Complication after formalin therapy	Improvement after formalin therapy
1	2	Nil	Partial improvement
2	1	Nil	Partial improvement
3	2	Nil	No improvement (later colostomy)
4	2	Nil	Complete improvement
5	1	Nil	Partial improvement
6	1	Nil	Partial improvement
7	2	Burning sensation	Complete improvement
8	2	Nil	Complete improvement
9	1	nil	Partial improvement
10	2	Nil	Complete improvement.

This prospective study involved 10 patients. All of them were female. Average age 50.9, age ranges from 33 to 72 years. Out of 10, nine patients suffered from cervical cancer and one patient suffered from ovarian cancer. Seven patients got EBRT and three patients got brachytherapy. All of these patients were previously treated conservatively for haemorrhage and as no improvement occurs were referred for formalin therapy. Average duration of bleeding after completion of radiotherapy 8.65 months, ranges from 15 days to 20 months. Average requirements of blood transfusions 6.9 units range from 0 to 20 units. Four patients improved after single Formalin therapy. Six patients need Formalin therapy for two sessions. No patient suffered from any significant complication after Formalin therapy. Complete improvement of bleeding in four patients, partial improvement in five patients and one patient has no improvement and later required a diversion colostomy.

Discussion

Hemorrhagic proctitis caused by radiation therapy affect less than 10% of patients irradiated for pelvic tumors.[8] Cervical cancer is a common disease in our country. A majority of patients are treated with conventional RT which is associated with much higher toxicity to normal

tissues in comparison to conformal RT techniques such as IMRT. External beam radiation studies have seen incidence rates of radiation proctitis range from 2% to 39% depending on the severity/grade of proctitis, whereas IMRT studies have seen incidence rates from 1% to 9%.[9]

While CRP could cause a constellation of symptoms such as tenesmus, diarrhoea, constipation, and bleeding, the most clinically troublesome feature happens to be bleeding. As anaemia is an established problem in Bangladeshi patients due to nutritional factors CRP could exacerbate it to severe extents. It is not uncommon for patients with CRP to present with severe anemia requiring multiple blood transfusions. While mild bleeding in CRP patients can be treated with medications including sucralfate, antidiarrhoeals, steroid enema, and hyperbaric oxygen, it is to be noted that moderate to severe bleeding in CRP patients seldom responds to these.[10]

In contrast to APC and YAG-laser coagulation, the use of formalin application for CRP involves negligible expense. The biological rationale happens to be the fact that formalin seals radiation-induced telangiectatic neovasculature in radiation-damaged tissues through a process of chemical cauterization. Reported success rates range from 60% to 100% in various reports.[11-13] While studies have utilized formalin application with concentrations ranging from 3.6% to 10%, it must be noted that lower concentrations were as efficacious as higher concentrations, while also being associated with lesser toxicities. Reported toxicity in literature includes acute colitis, which is usually transient.[14]

In our study, topical application of formalin with a concentration of 4% has an efficacy of 90% with complete or partial response. There is a lack of control group in our study and these results has to be accepted as preliminary based on our experience on hemorrhagic proctitis. Our results show that rectal formalin application is an effective, easy and cheap treatment method for bleeding from radiation induced proctitis.

Conclusion

In our study we found 4% formalin application to be safe, moderately effective and a cheap alternative, with no signification complications in treating radiation induced haemorrhagic proctitis. We can recommend 4% Formalin application as second line treatment for radiation induced haemorrhagic proctitis when medical management fails.

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Original Article

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Primary Mediastinal Tumors in Children: Experience of a Single Institute of Bangladesh with 71 Cases

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ABSTRACT

Introduction: *Mediastinal tumors are not uncommon in the pediatric population and pose a diagnostic as well as therapeutic dilemma to clinicians. It can originate from any mediastinal organ or tissue such as lymphatic, thymic, neurogenic, germinal, or mesenchymal tissue.* ***Methods:*** *Total 71 children with primary mediastinal masses under 18 years of age were diagnosed at the Department of Pediatric Hematology and Oncology (PHO) of National Institute of Cancer Research and Hospital (NICRH) between 2014 and 2018. It was a descriptive cross sectional study. Children were evaluated for the epidemiological characteristics, clinical features and diagnostic outlines. The patient's sex, age of onset, initial clinical symptoms and tumor types were analyzed. Secondarily correlation was observed between different groups of tumors.* ***Results:*** *Total mediastinal tumors were 71 in number which was 3.17% (71/2242) of total childhood tumors. Median age of onset was 11 years (range: 1–17 years) with 59.15 % male. Most of the patients were from Dhaka division (25.35%) followed by Mymensingh division (18.31%). Median diagnostic delay was 3.51 months. The most common tumor group was hematological tumors (53.52%) and most common tumor was non-Hodgkin's lymphomas (46.48%), followed by Primitive Neuro-Ectodermal Tumors (PNET)/Askin Tumor (12.68%). Hodgkin diseases (HL), Neuroblas-toma and germ cell tumors were 5.63%. Thymoma, Muco-epidermoid carcinoma of lung, Fibrosarcoma each was 2 in number. Among 71 cases 90.14 % tumors were malignant in nature, with only 7 cases being benign in nature. Common symptoms and signs of mediastinal tumors include breathing difficulty and productive cough (71.83%) followed by fever (70.42%), chest pain (54.93%), chest deformity (40.85%), upper limb weakness (9.86%). Common locations of tumors were anterior mediastinal with Non-Hodgkin Lymphoma (NHL), Teratoma and HL. Most common complication was pleural effusion (50.70%) followed by pericardial effusion (7.04%) with 60.56% tumors were metastatic. There was no statistical difference between hematological tumors and non-hematological tumors.* ***Conclusion****: In children, malignant mediastinal masses are more common than benign mediastinal masses. Non-Hodgkin's lymphoma and PNET were the two most common mediastinal tumors.*

Key words: *Primary mediastinal tumors, Children, Bangladesh*

Introduction

Primary mediastinal malignancies are rare tumors originating from any mediastinal organ or tissue, such as thymic, neurogenic, lymphatic, germinal, or mesenchymal.[1] The tumors encounter in clinical practice, and the source of origin of these masses can be an enigma for the clinicians, which can be neoplastic, congenital, or inflammatory in nature.

The mediastinum is the most common site of chest masses in children.[2,3] The masses are of diverse origin and pathogenesis, arising from virtually any organ or tissue in the mediastinum. The differential diagnosis includes neoplastic, developmental, inflammatory, traumatic, and cardiovascular tumors, pseudotumors, and nonpathological variations in the growth and development of normal thoracic structures.[4] The mass may occur at any age, from the neonatal period through adolescence, with protean signs and symptoms that reflect both the primary pathologic condition and functional compromise of involved organs.[5]

Most of mediastinum tumors are malignant in nature. For instance, thymomas and lymphomas can arise from the anterior mediastinum. Germ cell tumors mainly arise from the middle mediastinum, while neurogenic tumors often originate from the sympathetic nerve chains or spinal roots of the posterior mediastinum.[6] Mediastinum compartmentalization help to narrow the differential diagnosis of newly detected mediastinal tumors, but it may be difficult to localize a rapidly growing tumor to its anatomic compartment because it can spread from one space to another or involve the entire mediastinum.[1]

Most pediatric patients with mediastinal masses are symptomatic as compared to adults.[6] Symptoms may result from local compression or invasion of adjacent mediastinal structures.[7] For example, local compression to the trachea may cause severe breathing problems. Dysphagia is the result of esophageal narrowing. Superior vena cava syndrome is caused by obstructed venous return.[8] Gun et al. reported common symptoms in patients: cough, dyspnea, fatigue, fever, abdomen and back pain, and neurological symptoms **1**. In children compared to adults, rapidly growing mediastinal tumors can easily cause compression of the airway and blood vessels because of the smaller size of the thoracic cavity. Therefore, life-threatening conditions can rapidly develop, such as Acute Respiratory Distress Syndrome (ARDS) and Superior Vena Cava (SVC) syndrome in children. [9-11]

To know about mediastinal masses, it is necessary to understand the importance of the mediastinum as a central area of the thorax and its vital structures. To the best of our knowledge, there have been no prior studies involving pediatric populations focusing on the clinical presentation of mediastinal tumors in Bangladesh. So, this study was conducted to assess the epidemiologic profile, clinicopathological features, and histopathological findings in patients presenting with mediastinal masses in a tertiary care hospital over a period of 5 years

Materials and Methods:

It was a descriptive cross-sectional study. Data were collected from patients aged less than 18 years with pathologically proven mediastinal tumors diagnosed by tissue biopsy, and bone marrow study from January 2014 to December 2018 in a tertiary care hospital of Bangladesh, National Institute of Cancer Research and Hospital (NICRH) during admission or at the edge of enrollment. The information was collected from the description of patients/parents and went through all previous papers, including prescriptions of General Practitioners, to get medical information. Data such as patient's sex, age of disease onset, initial clinical symptoms, investigations like x-ray, CT scan, and hematological and biochemical reports to identify airway obstruction, pleural effusion, pericardial effusion, superior vena cava (SVC) syndrome were collected in a preformed data sheet. Tissue from core biopsy, Bone marrow, or operated sample was considered for histopathological, flow cytometry and /or immuno-histochemical study.

Mediastinal tumors were classified according to *the International Classification* of *Childhood Cancer* (ICCC-3), but for comparison with other tumors, Leukemia and Lymphoma were described as Hematological malignancies. The primary outcome was to depict epidemiologic data of pediatric mediastinal tumors. The secondary aim was to determine any correlations between the clinical symptoms of hematological tumors and non-hematological malignancy. The Pearson chi-square test or Fisher exact test was used as appropriate for categorical variables. All of the tests were 2-tailed, and a P value of <.05 was

considered statically significant. All data were analyzed using SPSS software.

Inclusion criteria:

- All patients referred to our department aged 0 to <18 years.
- CT scan of the thorax showing well defined mediastinal mass.
- Confirmed the diagnosis by mediastinal tissue biopsy or/and immunohistochemistry.

Exclusion criteria:

- Vascular lesions evident on contrast CT scan, i.e., dilated pulmonary artery, vascular aneurysm.
- Tumors which have extra-thoracic manifestations like neck lymph nodes.
- Pathological report of mediastinal mass from FNAC sample.

Result:

A total of 71 patients were evaluated in our study, which is 3.17% (71/2242) of total childhood tumors. Among them, hematological malignancy was 38 cases, and non-hematological malignancy was 33. The median age of onset was 11 years (age range: 0–17 years). Male Female ratio was 1: 0.69. The common age of presentation was 10-17 years (64.79%). Most of the patients came from the Dhaka division (N-18, 25.35%), followed by Mymensingh (N-13, 18.31%), Chattogram (N-11, 15.49%), Barisal (N-9, 12.68%), Rangpur (N-6, 8.45%), Rajshahi and Sylhet (N- 2, 2.82%). More than 90 % (N-64) of patients were village dwellers. The majority of our patients were poor (N-60, 84.5%), and the rest were middle-income groups. The mean diagnostic delay was 3.51 months. Hematological and Non-hematological data were depicted in Table-I.

Table-1: Baseline clinical characteristics of 71 mediastinal Masses

Sl.no	Variables and address of patients	Number (%)	Hematological Tumors (%)	Non-hematological (%)	*p*-value
1.	**Age**				
	Mean age (yrs.)	11.00	11.43	10.5	0.23
	Range in Yrs.	01-17	2.5–17	1-17	
	Age 0-4 yrs.	11 (15.49)	3 (4.23)	8 (11.26)	
	Age 5-9 yrs.	14 (19.72)	9 (12.68)	5 (7.04)	0.145
	Age 10-17 yrs.	46 (64.79)	26 (36.62)	20 (28.17)	
2.	Male : Female	1: 0.69 (N-42/29)	1:1(N-19/19)	1: 2.3 (N-23/10)	0.092
3.	**Division**				
	Dhaka	18 (25.35)	8 (11.27)	10 (14.08)	
	Mymensingh	13 (18.31)	8 (11.27)	5 (7.04)	
	Chattogram	11 (15.49)	2 (2.82)	9 (12.67)	0.133
	Khulna	10 (14.08)	6 (8.45)	4 (5.63)	
	Barisal	9 (12.68)	6 (8.45)	3 (4.23)	
	Rangpur	6 (8.45)	5 (7.04)	1 (1.41)	
	Rajshahi	2 (2.82)	2 (2.82)	0	
	Sylhet	2 (2.82)	1 (1.41)	1 (1.41)	
4.	Village dweller	64 (90.14)	34 (47.89)	30 (42.25)	0.840
	Town dweller	7 (9.86)	4 (5.63)	3 (4.23)	
5.	**SES-**Poor:Mid:Rich	60:11:0	30: 8: 0	30: 3: 0	0.165
6.	**F/ H of Cancer**				
	Present	1 (1.41)	1 (1.41)	0	
	Absent	70 (98.59)	37(52.11)	33 (46.48)	
7.	Diagnostic delay (in Months)	Mean- 3.51	Mean 2.92	Mean-4.18	0.211

SES- Socio-economical Condition

Mediastinal tumors were classified (Figure-1 and Table: 2) according to *International Classification* of *Childhood Cancer* (ICCC-3). Most common tumors were Hematological malignancy (Leukemia 1.41%, Lymphoma 52.11%), followed by Soft tissue sarcomas (N-16, 22.53%), Epithelial neoplasms (N-7, 9.86%), Neuroblastoma (N-5, 5.04%), Germ cell tumors (N-4, 5.63%), Renal tumor ((N-1, 1.41%).

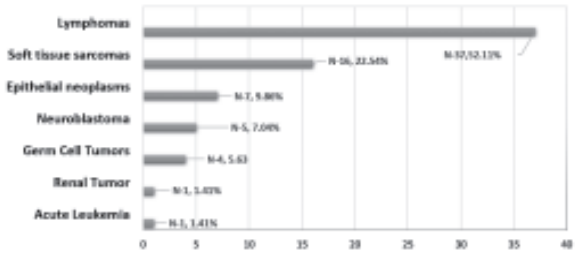

Fig.-1: *Number and percentage of mediastinal tumors.*

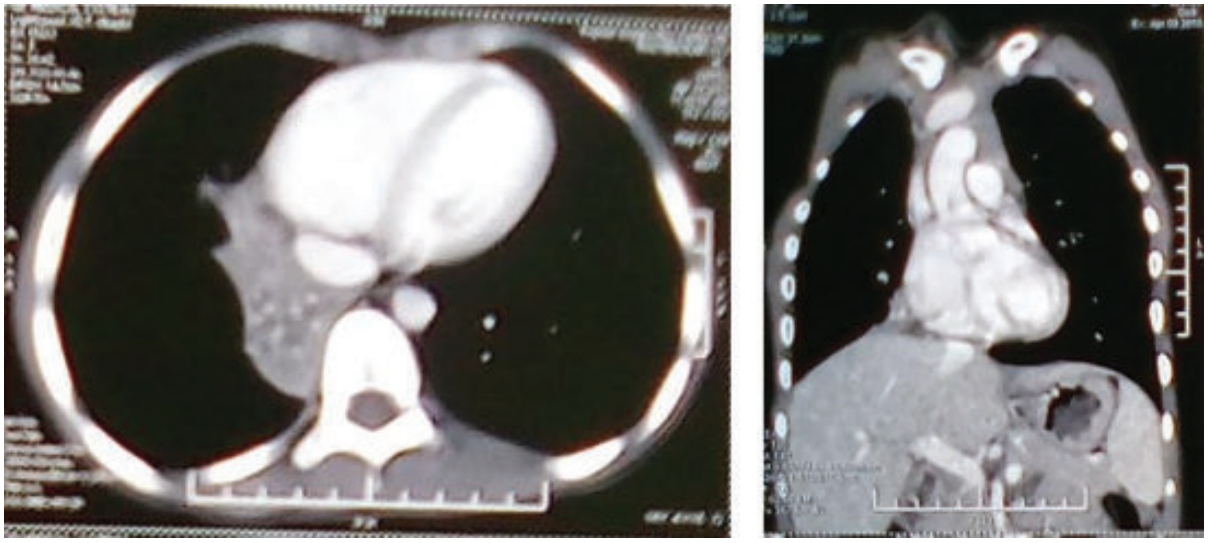

Fig.-2a and 2b: *Computer tomography (CT) imaging of chest showing a middle mediastinum mass – A rare tumor: Mucoepidermoid carcinoma (MEC).*

Table- II: depicts the most common type of mediastinal tumors in this study were lymphomas (33/71, 46.48%), followed by Primitive Neuro-Ectodermal Tumors (PNET)/ Askin Tumor (9/71, 12.68%). Hodgkin disease (N-4, 5.63%), Neuroblastoma 5.63% (4/71). Thymoma, Mucoepidermoid carcinoma of the lung (Fig.2), and Fibrosarcoma each were 2 (2.82%) in number. Rhabdomyosarcoma, Malignant peripheral nerve sheath tumor (MPNST), Spindle cell sarcoma, Desmoplastic small round cell tumor (DSRCT), Adenocarcinoma, Carcinoid Tumor, Squamous cell carcinoma, Wilms Tumors, Ganglioneuroma was one in number (1.41%). One patient was leveled as soft tissue sarcoma, as it was not possible to yield a definitive diagnosis even through immunohistochemistry.

Among 71 cases, 90.14 % (N-64) of the mediastinal tumors were malignant, with only 7 (9.86 %) cases being benign.

Clinical presentations of children with mediastinal malignancy have been demonstrated in Table III. Common symptoms and signs of mediastinal tumors include breathing difficulty and productive cough (N-51, 71.83%), followed by fever (N-50, 70.42%), chest pain (N-39, 54.93%), Chest deformity (N-29, 40.85%) and upper limb weakness (N-7, 9.86). Other less frequent symptoms were hemoptysis (N-4, 5.63%) and superior vena cava syndrome (SVCS) (N-3, 4.23%). Hypothyroid features were in 2.42% of cases. B-Symptom was one in number.

Table II: Mediastinal tumors, number & percentage

Sl.	Tumor Group	Tumor types	Frequency (%)
1.	Hematology Tumors (N-38)		53.52
	a) Leukemia	Acute leukemia (ALL)	1(1.41)
	b) Lymphomas	Non-Hodgkin Lymphoma	33(46.48)
		Hodgkin Lymphoma	4(5.63)
2	Soft tissue and other	PNET/Askin Tumor (6+3)	9(12.68)
	extraosseous sarcomas (N-16)	Fibrosarcoma	2(2.82)
		Rhabdomyosarcoma	1(1.41)
		MPNST	1(1.41)
		Spindle cell sarcoma	1(1.41)
		DSRCT	1(1.41)
		Soft tissue Sarcoma	1(1.41)
3.	Carcinomas and other Malignant	Thymoma	2(2.82)
	Epithelial Neoplasms (N-7)	Adenocarcinoma	1(1.41)
		Carcinoid Tumor	1(1.41)
		Sq.cell carcinoma	1(1.41)
		MEC of Lung	2(2.82)
4.	Renal Tumor (N-1)	Wilms Tumors	1(1.41)
5.	Germ cell tumors (GCTs) (N-4)	Teratoma	4(5.63)
6.	Neuroblastoma and other	Neuroblastoma	4(5.63)
	peripheral nervous cell tumors (N-5)	Ganglioneuroma	1(1.41)
7.	Ratio	Malignant	64(90.14)
		Benign	7 (9.86)

Table III : *Clinical features of mediastinal Tumors*

Sl.no	Signs and Syndromes	Total (%)	Hematology (%)	*Non-Hema (%)*	*p-value*
1.	Fever	50(70.42)	31(43.66)	19(26.76)	0.209
2.	Cough	51(71.83)	31(43.66)	20(28.17)	0.124
3.	Respiratory distress	51(71.83)	29 (40.85)	22(30.99)	0.61
4.	Chest Pain	39(54.93)	19(26.76)	20(28.17)	0.12
5.	Chest deformity	29(40.85)	14(19.72)	15(21.13)	0.341
6.	Upper limb weakness	7(9.86)	3(4.23)	4(5.6)	0.091
7.	Hypothyroid features	2(2.42)	2 (2.84)	0	-
8.	Hemoptysis,	4(5.63)	1(1.41)	3(4.23)	0.0
	B-Symptoms,	1(1.41)	1(1.41)	0	-
	SVCs	3(4.23)	1(1.41)	2(2.82)	0.286

Table IV : Procedures for diagnosis of mediastinal Tumors

Sl.no	Investigations/Procedure	Total (%)	Hematology (%)	*Non-Hemato (%)*
1.	Chest X-ray (CXR)	71(100)	38(53.52)	33(46.48)
	Ultrasonogram (USG)	5(7.04)	1(1.41)	4(5.63)
	Computed tomography (CT) scan	66 (92.96)	35(49.30)	31(43.66)
2.	**Tissue Biopsy Collection-**			
	USG guided	12(16.90)	11(15.49)	1(1.41)
	CT guided	52 (73.24)	27 (38.03)	25(35.21)
	Bone Marrow study	38(53.52)	30(42.25)	8(11.27)
	Surgery and open biopsy	7(9.86)	0	7(9.86)
3.	Immunophenotype/ IHC	17(23.94	7 (9.86)	10(14.08)

Diagnostic work-up described in Table-IV. Tissue was collected for histopathological examination by using USG guided devices (N-12, 16.90%), CT guided devices (N-52, 73.24%) and surgical intervention (N-7, 9.86%). Patients were evaluated by bone marrow study in 53.52% (N-38) of cases and immunophenotype or immunohistochemistry (IHC) in 23.94 % (N-17) cases.

The individual tumor occupying the mediastinal anatomical area was shown in Table-V. Summarizing the table, most common anterior mediastinal tumors were Non-Hodgkin Lymphoma (NHL), Teratoma and Hodgkin Lymphoma. Common Middle mediastinal tumors were NHL, HL and Mucoepidermoid carcinoma and posterior mediastinum tumors were Neuroblastoma, NHL, MPNST and PNET. Superior mediastinum with Wilms Tumor, Adenocarcinoma, ALL, STS and PNET. Among 71 cases 32.39% (N-23) patients involved more than one side.

Table- V: Mediastinal Localization of the Tumors

Histology	Anterior	Middle	Posterior	Superior	>1 side
Non-Hodgkin Lymphoma (NHL)	14	5	2	0	12
Teratoma (GCTs)	4	0	0	0	0
Hodgkin Lymphoma	2	1	0	0	1
Fibrosarcoma/Spindle cell sarcoma/					
RMS/Carcinoid Tumor/Sq cell ca	1	0	0	0	0
Neuroblastoma	0	0	2	0	2
Askin	0	0	0	0	3
PNET	0	0	1	1	4
MEC of Lung	1	1	0	0	0
Acute leukemia (ALL)/ STS	0	0	0	1	0
DSRCT /Ganglioneuroma	0	0	0	0	1
Adenocarcinoma/Wilms Tumor	0	0	0	1	0
MPNST	0	0	1	0	0
Thymoma	2	0	0	0	0

Table- VI: *Complications of mediastinal Tumors*

Sl. no	Location, diagnosis & complications	Total (%)	Hematology (%)	Non Hemato (%)	*p*-value
1.	Effusion				
	i) Pericardial	5(7.04)	4 (5.63)	1(1.41)	0.673
	ii) Pleural	36(50.70)	23 (32.39)	13(18.31)	0.276
2	Calcification	1(1.41)	0	1 (1.41)	
	Lung collapse	3 (4.23)	2 (2.82)	1 (1.41)	
3.	Pneumothorax	1 (1.41)	1 (1.41)	0	
4.	Metastasis	43(60.56)	28 (39.44)	15 (21.13)	0.135
	No metastasis	28(39.44)	10(14.08)	18 (25.35)	
5.	Metastatic sides				
	i) Plural	36(50.70)	23(32.39)	13 (18.31)	
	ii) Pericardium	5 (7.04)	4 (5.6)	1 (1.41)	
	iii) Lung	3 (4.23)	2 (2.82)	1 (1.41)	
	iv) Rib	3 (4.22)	1 (1.41)	2 (2.82)	
	v) Liver	1(1.41)	0	1 (1.41)	

NB: Some tumors did metastasis in more than one side

Most common complications of mediastinal tumors (Table- VI) were effusion in pleural cavity (50.70%, N-36) and followed by pericardial sac (7.04 %, N-5). Lung collapse and calcification was one in both cases (1.41%). Malignant tumors were 60.56% (N-43) metastasis with Pleura, Pericardium, Lung, Rib and liver involvement.

Discussion

Mediastinal masses have always been a diagnostic as well as therapeutic dilemma for medical professionals. Most of the clinical studies on mediastinal masses are retrospective single institutional studies mainly based on case records.[12, 13] Temes et al.[14] reported 0.2% adult patients with tumors suffered from mediastinal tumors. In the present study 3.17% (71/2242) of total pediatric tumors presented as mediastinal masses. Median age of onset was 11 years (age range: 0–17 years). Male Female ratio was 1: 0.69 (42/29). Liu at al.[15] from a Chinese institution found the same median age of 11 years. A study from Taiwan by Chen et al [8] found the median age of onset was 13 years (Range 0-17 years), male: female ratio was 1: 0.33. Common age of presentation of our children was 10-17 years (64.79%), where Tansel et al. [16] reported 11-17 years were the common presenting age.

Major number of the patients came from Dhaka division (N-18, 25.35%), followed by Mymensingh, (N-13, 18.31%), Chattogram (N-11, 15.49%), Barisal (N-9, 12.68%), Rangpur (N-6, 8.45%), Rajshahi and Sylhet (N-2, 2.82%). Most possible cause of this disparity of patient's number may be the distance of the patient's resident from our center. Maximum patients of our study were economically poor (N-60, 84.50 %) and village dwellers (N-64, 90.14%). In a previous data of our Institute by Jabeen et al. [17] found that most of the children with cancer came from the rural areas (67%) compared to 33% from urban areas. Like Bangladesh, in Pakistan 78% patients of mediastinal masses belonged to lower socio-economic class. [18]

Early diagnosis remains a key factor and a fundamental goal in pediatric oncology and delayed diagnosis may also be associated with huge economic cost.[19] We define "Diagnostic delay" that means from start of symptoms to final diagnosis or start of treatment. In our study diagnostic delay was 3.51 months (Range- 6 to 144 months). Our findings correlate with the data of a previous study of our institute by Begum et al [20], where she reported that more than 70% of the pediatric patients had to wait for more than 90 days for the treatment. Chukwu et al from Nigeria found the median total lag

time to diagnosis of cancer was 15.8 weeks.[21] But in the developed nation like Singapore diagnostic median total delay was 5.3 weeks (range 0.1–283.1 weeks).[22] Diagnostic delayed depend on parent's understanding about the diseases, parents' economical condition, type of cancer, health delivery system.

We classified the tumors according to ICCC-3 (Table-2 and Fig 1) but for comparison with other tumors, Leukemia and Lymphoma were described as Hematological malignancy. Among 71 cases, most common mediastinal masses were hematological malignancy (N-38, 53.52%) cases and 33 (46.48%) cases were non hematological. Few studies showed hematological malignancy forming a huge burden (47.5%) of the pediatric mediastinal masses.[8] But in a study by Grosfeld et al. [23] founded less (N-37, 42.86%) number of hematological malignancy in childhood mediastinum. Our study correlates with the first one.

Among the hematological malignancy most common mediastinal malignancy in the present study was Non-Hodgkin lymphoma (N-33, 46.48%). Taiwanese investigator Chen et al found same incidence rate (47.5%) in a study.[8] Juanpere et al.[24] reported lymphoma represents 50% in children. McCarville et al. [25] reported about half of the children with non-Hodgkin lymphoma present with an anterior mediastinal mass. Our finding (42.42%,14/33) was consistent with this data. Previous study reported pleural effusions occur in 50–75% of those with lymphoblastic lymphoma [26, 27] which was consistent with our findings (60.60%, 20/33) about NHL.

Other hematological malignancies were Hodgkin lymphoma and acute leukemia. The present study determined only 5.63% (N-4) cases as HL. In some studies Hodgkin disease have been reported to be 33% to 56% of pediatric mediastinal lymphomas[28,29] and Panda et al. reported 27%.[30] On the other hand acute leukemia is very less in number in pediatric mediastinum. We have one case of ALL which was in superior mediastinum with pleural effusion but not SVC. Most of the case are T-cell leukemia present with an anterior mediastinal mass and pleural effusions.[31] Arya et al. [32] reported aggressive tumors like T cell acute leukemia caused superior mediastinal syndrome.

Soft tissue sarcoma was the second most (22.54%) common group (ICCC-3) of mediastinal tumors which included PNET/Askin Tumor (12.68%), Fibrosarcoma (2.82%) and Rhabdomyosarcoma, MPNST, Spindle cell sarcoma, DSRCT, Soft tissue Sarcoma (STS) was one in number (2.82%). Sarcomas have been reported at 2% to 3% of pediatric mediastinal masses.[23] But another study from Turkey found sarcoma at 15%, a much higher incidence than previously report.[1] Soft tissue Sarcoma and spindle cell sarcoma each were one in number and they were not possible to yield definitive diagnosis even through immunohistochemistry. We have no speculation on this fact of the huge incidence of soft tissue sarcoma.

Second common tumor specific type of tumor was primitive neuroectodermal tumor (PNET), which was 12.68% (N-9) of total mediastinal tumors. In the previous study by Burt et al. [33] found that about 17% of malignant tumors of the chest are of the Ewing sarcoma family of tumors and 11.3% found by Shamberger and colleagues.[34] Our findings were consistent with this data. All the PNET of our study appeared in posterior mediastinum except one which was from middle mediastinum.

Infantile fibrosarcoma of the lung in infants and children is very rare, and this entity is referred to as primary bronchopulmonary fibrosarcoma.[35] More than 80% of cases occur within the 1st year of life, and a slight predominance in male infants has been reported.[36] In our study fibrosarcoma were 2.82 % in male sex.

Nerve sheath tumors consist of schwannomas, encapsulated tumors lacking nerve fibers, and neurofibromas. About 5% of these tumors undergo malignant degeneration and about half of these are seen in patients with type 1 neurofibromatosis.[37, 38] This Malignant peripheral nerve sheath tumors (MPNST) are rare pediatric tumors and its presence in mediastinum is also uncommon. We documented one patient (1.41%) in the study.

Primary pulmonary rhabdomyosarcoma is extremely rare. To best of our knowledge, only 26 cases of pediatric pulmonary RMS have been reported in literature till 2020.[39-42] We reported a child with primary rhabdomyosarcoma of the lung, showing an embryonal type.

Primary spindle cell sarcoma (SCS) is an extremely rare entity and one of the least reported tumor.[43] Only a handful of cases have been reported around the world from variety of body parts.[44, 45] of adult patients. We got one case (1.41%) of mediastinal SCS at the early of

our study when immunohistochemistry was not available in our country.

Desmoplastic small round cell tumor (DSRCT) is a rarely-seen distinct tumor with high-grade malignancy been less than 400 cases reported worldwide, with 95% of cases found in the abdominal cavity.[46] There have been a few cases of pulmonary and pleural DSRCT.[47, 48] A patient with mediastinal DSRCT admitted to our hospital with pleural effusion.

Primary mediastinal germ cell tumors (GCTs) are rare and located in anterior mediastinum. These tumors constitute 10% of all mediastinal masses in children.[2] About 5% of all extragonadal germ cell tumors originate from the mediastinum in children younger than 15 years.[49, 50] Our study revealed 5.63% (N-4) GCTs, all of which were situated in anterior mediastinum and all the children were male. Though it has been reported by Barksdale et al.[51] that 20% of mediastinal GCTs are malignant, we did not diagnose any malignant GCTs in this study.

Thymomas, which represent less than 1% of all mediastinal tumors, are rare in the pediatric age group. A study by Gun et al.[1] thymic pathologies were more frequent than the literature were 4% of mediastinal tumors. In the present study Thymoma was 2.82% involving the anterior and middle mediastinum.

Mediastinal neuroendocrine tumors (NETs) are very rare. They have been estimated to account for approximately 2%-4% of all anterior mediastinal neoplasms in adult.[52] In pediatric population its incidence is nine of the 4,656 (0.19%) children with cancer and about 0.02% of mediastinal mass.[53] In 30% cases Carcinoids presented with calcification.[54] We have reported one case without calcification.

Primary mediastinal adenocarcinoma is a rare malignancy that can arise from normal or ectopic tissue in the mediastinum.[55] These normal organs in the mediastinum, such as the thymus and the lymph nodes.[56] No separate literature regarding pediatric Primary mediastinal adenocarcinoma are available. We admitted a boy of 10 years with a mass (revealed adenocarcinoma) in the superior mediastinum mass with a calcified nodule.

Mucoepidermoid carcinoma (MEC) of the lung is an uncommon tumor type, arising from minor salivary gland tissue of the trachea bronchial tree. This occurs in patients with an age range from 3 years to 78 years [57, 58] but it is not common in the lungs, particularly in children, accounting for only 0.1-0.2% of primary lung cancers.[59, 60] We have reported two cases (2.82%) out of 71 mediastinal tumors.

Wilms tumor within mediastinum is an extremely rare lesion. Very few studies reported such a lesion. Badillo et al.[61] report a case of an 18-year-old man with a Wilms' tumor arising within a mediastinal teratoma. Gun et al. reported 1 case (0.83%) out of 120 pediatric mediastinal tumors.[1] The present study reported one case.

Majority of pediatric mediastinal neuroblastomas occur most often in the first 3 years of life, followed by less common tumors like ganglioneuroblastomas; the rest are ganglioneuromas, occurring in older children.[62] In the study. Chen et al.[1] reported 12.5% 0f neuroblastoma and 2.5% Ganglioneuroma of Taiwanese children. But in our study Neuroblastoma was 5.63% and Ganglioneuroma 1.41%, both were located in the posterior mediastinum.

Benign tumor of the present study was 9.86% (N-7) which is a relatively lower incidence than other large-scale studies of a single institute [23] but Chen et al.[1] reported 90% of malignant mediastinal masses in the pediatric population of Taiwan, which is consistent with our data.

Malignant lesions are more symptomatic in the form of malaise, unexplained fever and anorexia in comparison to benign lesions. All of the patients of our study presented with symptoms. Previous study reported the common clinical presentations of pediatric mediastinal mass were respiratory symptoms like cough and dyspnea in 60.7%, fever in 25% [16] but our study reported breathing difficulty and cough were in 71.83%, followed by fever in 70.42% and chest pain in 54.93%. Chen et al.[1] from Taiwan reported lower incidence of fever (30%), cough (47.5%), dyspnea (65%) and chest pain (27.5%). The low incidence of clinical features of Chen et al. study can be explained only by early diagnosis of mediastinal masses in developed world. The other findings of our study were upper limb weakness (9.86%), hemoptysis (5.63%), SVC (4.23%), hypothyroid features (2.42%) and B-Symptom (1.41%). No statistical difference was found in hematological and non-hematological groups.

In our study, the introduction of computed tomography (CT) for diagnosis has increased (92.96%) significantly in cancer diagnosis. None of our patients evaluated by magnetic resonance imaging (MRI), which is an excellent tool for assessment of mediastinal lesions owning to its clear soft tissue image resolution and direct multiplanar imaging.[63] Though CT guided FNAC is highly sensitive (95.2%) and accurate (93.5%) in diagnosing mediastinal masses.[64]

About 16.90% tissue of our study was collected by USG guided FNAC. Rest of the tissue was collected by CT guided (73.24%) core biopsy and surgical intervention (9.86%). Bone Marrow studies were done in 53.52% of cases, mostly hematological malignancy. Immunophenotype or immunohisto-chemistry (IHC) is a costly test in our country and was done in 23.94 % cases.

In a study conducted by Aroor et al.[65] mediastinal masses were most commonly found in the anterior mediastinum (42.86%) followed by middle mediastinum (11.43%), posterior mediastinum (8.57%), and multiple compartments (37.14%) which correlate our study as 30.99% tumors were in anterior mediastinum, 9.86% in middle mediastinum 8.45% in Posterior mediastinal masses and 4.23% in superior mediastinum. Majority tumors (32.39%) of our study were located in two or more mediastinum. Gun et al.[1] revealed 43.8% (53/120)) tumors were located in the posterior mediastinum, followed by 37 (31.4%) in the anterior and 30 (24.7%) in the middle mediastinum. This disparity of tumor location with Gun et al is difficult to explain.

Most common complications of our study were effusion in pleural cavity 50.70% (N-36) followed by pericardial effusion 7.04 % (N-5), Lung collapse and rib erosion in 4.23% cases. Pneumothorax (NHL) and calcification (PNET) was one in both cases (1.41%). Chen et al [8] reported pleural effusion 54.5% and pericardial effusion 54.5%. Pneumothorax is a rare presentation of pediatric mediastinal tumors. Common causes associated with the development pneumothorax includes lymphoma and metastasis.[66] We reported 3 cases of rib involvement due to PNET, DSRCT and NHL.

In a study on mediastinal masses of adults Whooley et al. [67] reported distant metastases were present at diagnosis in 11% (14 of 124). But in our study the incidence of metastasis at diagnosis of pediatric mediastinal tumors were 60.56% (N-43), with Pleura 50.70% (N-36), Pericardium 7.04 % (N-5), Lung and Rib 4.23% (N-3), Live 1.41%. Some tumors metastasis in more than one side. Most of the metastasis (N-28, 39.44%) were due to hematological malignancy.

Conclusion:

Primary pediatric mediastinal malignancies are not rare in infants and children. Most common tumors were Lymphoma, followed by PNET and Hodgkin lymphoma. More than 90% of tumors were malignant in nature. Age of presentation and location was 10-17 years and anterior mediastinal respectfully. Incidence of fever, cough and dyspnea in our patients were high, perhaps due to diagnostic delay. Very uncommon soft tissue sarcomas and very rare carcinomas were in our findings. Primary Wilms tumors and malignant peripheral nerve sheath tumors in mediastinum are extremely rare in the pediatric population. No statistical significance was shown in Hematological tumor and Non-Hematological tumors.

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Original Article

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Incomplete Clinical Information in a Surgical Pathology Requisition Form: The Extent and Impact on Results

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Abstract

Introduction: *Incomplete clinical information in the surgical pathology requisition form may compromise the patient care by making the diagnosis difficult.* This study shows the frequency and *nature of the problems caused by inadequate clinical information provided on histopathology requisition.* ***Method:*** *This observational descriptive study was carried out at the histopathology department of National Institute of Cancer Research and Hospital. Data were collected from all the surgical pathology requisition form that were sent along with the specimens, over a period of four months from September 2019 to December 2019. Data were recorded by simple check list.* ***Results:*** *Out of 1509 requisition forms, anatomic sites of the specimen were absent in 52 (3.44%), type of the procedure to obtain the specimen was absent in 59 (3.9%), no clinical data was found in 134 (8.9%) and inadequate clinical information was present in 1092 (72.3%) of requisition form. Clinician's contact information was absent in 1490 (98.7%) of requisition forms. Out of 1509 surgical pathology cases, 566 (37.5%) required additional clinical information before the case could be completed. In 48 (3.2%) of the cases the diagnosis was substantially changed because of the additional clinical information and reporting delay occurred in 576(38.1%) cases due to inadequate clinical information.* ***Conclusions:*** *This study establishes the increased rate of cases with inadequate clinical information for diagnosis and document the extent of problem that caused by inadequate clinical information.*

Key words: *Histopathology Requisition form, Clinical information, Histopathology diagnosis*

Introduction

The surgical pathologist has a unique opportunity to start the journey from the beginning of a disease and its end stages. Surgical pathology heavily depends on clinicians and surgeons who are entirely aware of the specialty and provide essential clinical information to the pathologist to evaluate the histopathological diagnosis properly.[1]

Absent and incomplete clinical information in the histopathology requisition form is one of the most

common problems histopathologists face during reporting. The laboratory accreditation standards outlined by the College of American Pathologists and the Joint Commission on Accreditation of Healthcare Organisations require that each surgically removed specimen is accompanied by relevant clinical information. [2,3]

In this study, we analysed the frequency of present, absent and inadequate clinical information in a surgical pathology requisition form and its impact on histopathology reporting.

Materials and methods:

This descriptive observational study was carried out at the histopathology department of the National Institute of Cancer Research and Hospital. Data were collected from all the surgical pathology requisition forms sent along with the specimens for four months, from September 2019 to December 2019. A simple checklist recorded data. Clinical information in a different part of the requisition slip was analyzed. Requests for the Frozen section and review report examination were excluded from the study.

Working definition:

Inadequate clinical data: Cases were considered as inadequate clinical data that contained little pertinent clinical information.

No clinical data: Cases were considered as having no clinical data containing no and/or only demographic data and the specimen's name.

The following data were recorded for each case:

1. Anatomic site of the specimen
2. Type of the procedure to obtain the specimen
3. Nature of the disease process
4. Clinical history
5. Clinician's contact information

Results:

All (1509) histopathology requisition forms sent along with the specimens from September 2019 to December 2019 were analysed. Out of 1509 requisition forms, anatomic sites of the specimen were absent in 52(3.44%) cases. The type of procedure to obtain the specimen was absent in 59(3.9%) cases, and the clinician's contact information was absent in 1490(98.7%) of the request forms (Figure-1).

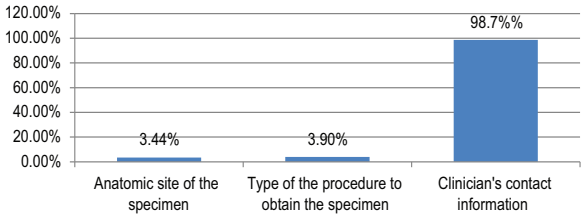

Fig-1: *Bar diagram showing frequency of nature of information that was absent in histopathology requisition forms (n=1509)*

Among 1509 histopathology requisition forms, adequate clinical information was present in 282(18.6%), inadequate clinical information was present in 1092(72.3%), and no clinical information was present in 135(8.9%) of requisition forms (Figure-2).

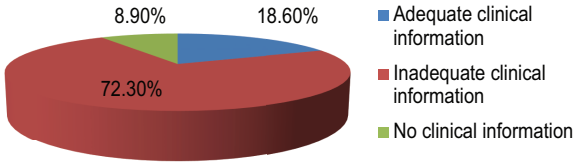

Fig.-2: *Pie diagram showing distribution of 1509 study requisition forms by the type of clinical information.*

Nine Hundred and Ninety-Three (65.8%) specimens were obtained by biopsy and curettage, and 516 (34.2%) specimens were obtained by resection. Specimens obtained by biopsies and curettage were significantly associated with a higher rate of (771, 77.6%) inadequate clinical information, resulting in a higher rate of delayed reporting (figure-3).

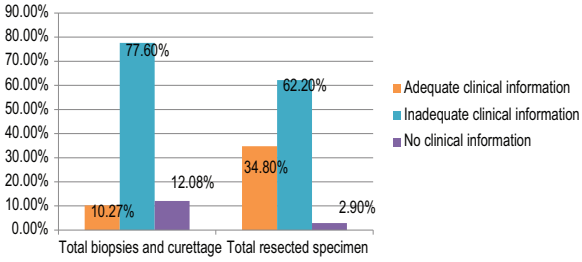

Fig.-3: *Bar diagram showing distribution of clinical information according to type of procedure in 1509 requisition forms*

According to the nature of the disease process, we found most of the cases were malignant neoplasm 1275 (84.4%), other disease conditions were 218 (14.4%), and no residual tumours were 16 (1.06%). Among the malignant cases, adequate clinical information was present in 242 (18.6%), inadequate clinical information was present in 923(72.3%), and no clinical information was present in 110 (8.6%) requisition forms (Figure 5).

Of 16 no residual tumour-diagnosed cases, only two requisition forms supplied the therapeutic and previous operative information.

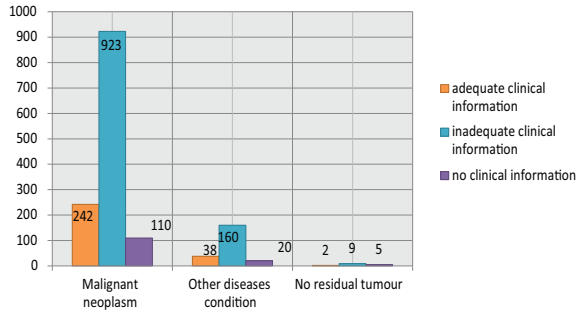

Figure-4: *Bar diagram showing distribution of clinical information according to nature of diseases process*

In this study we studied 1509 surgical pathology cases, of these 566 (37.5%) cases required additional clinical information before the case could be completed. In 48(3.2%) of the cases the diagnosis was substantially changed because of the additional clinical information. Reporting delay occurred in 576(38.1%) cases due to inadequate clinical information.

Discussion

In this study we examined the frequency of clinical information and severity of problems arising from inadequate and absent clinical information. In our study there were 134 (8.9%) cases where clinical data were absent. This is higher than the similar studies,[4,11] and lower than some other studies.[5,9,10]

To reach the final diagnosis histopathologist needs to be informed about all the relevant clinical information. In other words, the additional information was more often useful while the reasons for these findings are not clear.

In this study we studied 1509 surgical pathology cases, of these 566 (37.5%) cases required additional clinical information before the case could be completed which is much higher than another study which is 0.73%.[4]

In the current study, in 48 (3.2%) cases diagnoses were changed after receiving the additional clinical information. This result supported by some studies.[4,6] In a subsequent Q-Probes study, 10% of the amended reports resulted directly from additional clinical information.[7]

Insufficient clinical information causing an unnecessary delay in reporting for cases with inadequate clinical information, we found 566 (37.5%) cases with delayed report which is higher than similar study.[4]

Histopathological changes following chemotherapy and radiotherapy may lead to either complete response, partial response, no response or may be led to a progressive disease. So, patient who received radiotherapy and chemotherapy, without the history of therapy in the requisition paper led to an improper diagnosis. We found no residual tumor after neoadjuvant chemotherapy in 16 cases, among them 14 (87.5%) of cases have no therapeutic information in their requisition form and this result supported by similar study.[4]

Anatomic site of the tissue is one of the vital information that histopathologists need for reporting. But we found that about 3.4% samples were sent without mentioning the anatomic site of the specimen. This finding is supported by two study that not mentioned anatomic site in the requisition paper as 13% and 7.7%.[5,9]

Contact information of the clinicians are helpful to obtaining the additional clinical information. But in our study contact information of the clinicians were missing in 98.7% cases. Nearly similar findings have been described some studies.[5,9] For this reason pathologists are unable to collect the additional information for the proper diagnosis.

Conclusion

A full understanding of the clinical picture of a case helps the pathologist to make the most accurate diagnosis. This study establishes how commonly the clinical information are missing in the requisition form and the extent of problems caused by inadequate clinical information. In this study we studied 37.5% cases required additional clinical information before the case could be completed and in 3.2% of the cases the diagnosis was substantially changed because of the

additional clinical information. Reporting delay occurred in 576 (38.1%) cases due to inadequate clinical information. To reduce all of these problems there is no other choice than a representative clinical information in the requisition form. The highly recommended method of obtaining clinical information was through direct communication with the clinician or multidisciplinary team meeting in the institution, that may reduce the diagnostic error, turnaround time of reporting and ensure an effective patient management.

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Original Article

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Profile of Gynaecological Malignancies in NICRH: A Three-year Study from the Hospital Cancer Registry

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Abstract

Objectives: *Gynecological malignancies are the second most common cancer in females after breast cancer. Gynaecological malignancies are an important cause of female morbidity and mortality. The objective of this study was to find out the profile of gynaecological cancers in the National Institute of Cancer Research and Hospital (NICRH), Dhaka, from 2015 to 2017 regarding demography, the frequency of involvement at various sites, histologic subtypes, referral, and new cases. Methodology: It was an observational study based on retrospective data using hospital-based cancer registry records from January 2015 to December 2017. The study included all the gynecological cancer patients diagnosed using histological or cytological examination during that period and reported to the cancer registry. Result: Per hospital cancer registry records, 3505 confirmed cases attended NICRH from January 2015 to December 2017. Cervical cancer (77.62%) was the most common gynecological malignancy, followed by ovarian cancer (13.78%), uterine cancer (6.05%), and vaginal and vulvar cancer (1.85% & 0.65%, respectively). Squamous cell carcinoma was 92.90% in the cervix, while adenocarcinoma was found only in 6.40% of cases. In the case of carcinoma cervix, 1919(70.58%) cases were diagnosed as new, whereas prior treatment cases were 800 (29.42%). Cervical cancer mainly occurs in multiparous women (62.53%).*

Key words: *Cervical cancers, distributions, cancer registry, NICRH*

Introduction

Gynaecological malignancies are those involving the genital tract and include those of the ovary, cervix, uterus, vulva, vagina, and gestational trophoblastic neoplasia. These are the important cause of female mortality and morbidity.[1] New global cancer data suggest that the cancer burden has risen to 18 million cases and 9.6 million deaths per year with more than half of the cases residing in Asia.[2] They pose a significant burden on health resources in low-middle income countries. The diagnosis of malignancy is devastating for the patient not only in terms of anguish but also mortality and morbidity associated with it. The financial burden to the family and state is another worrisome problem.

The frequency of this gynaecological malignancy is different in different countries depending upon various factors like socioeconomic background, genetic pattern, and lifestyle.[3] Cervical cancer is the commonest gynaecological malignancy in developing countries and the most common type of cancer in women after breast cancer.[4] More than 85% of cases of cervical cancer occur in developing countries, where it accounts for 13% of all female cancer.[5, 6] The incidence and mortality of cervical cancer had declined in developed countries. The reasons are being effective cervical cancer screening programs and treatment of premalignant lesions of the cervix.

In developed countries, ovarian cancer is the commonest. It accounts for 4% of all malignancies affecting females.[7] It has the highest mortality rate in developing countries among all gynaecological cancers.[8] Two-thirds of cases of ovarian tumours present at the advanced stage. Endometrial cancer is the most common gynaecological malignancy in developed countries and its incidence is increasing.

Age and parity have a great relationship with gynaecological cancers. Endometrial cancer arises in postmenopausal women although 20-25% of endometrial cancer are diagnosed before menopause.[9] Ovarian cancer usually affects older women, though young women are more likely to suffer from germ cell cancers of the ovary than their older counterparts. Multiparous women have a high risk of cervical carcinoma while nulliparity is associated with an increased risk of endometrial and ovarian cancer.[10]

In Bangladesh, genital cancer is increasing day by day. The highest prevalence of genital tract cancer in underdeveloped countries is due to a lack of awareness, risky sexual behaviour, and the absence of population-based screening procedures, especially for cervical cancer.[11]

Materials and methods

We used three years of hospital records in this retrospective study from January 2015 to 2017. All the gynecological cancer patients diagnosed through histological and cytological examination during that period who reported to the cancer registry of NICRH were included in the study. A Checklist was used to extract relevant information from the cancer registry.

Results

There were 3503 patients diagnosed with gynaecological malignancy during the period from January 2015 to December 2017. Cervical cancer was found to be the commonest malignancy in 2719 (77.62%) patients, followed by ovarian cancer in 483 (13.79%) patients. The majority patients of with carcinoma cervix and ovarian cancer presented at advanced stages. The mean age of cervical cancer was 48.14±10.95 to 49.56+/-11.04 and ovarian cancer was 42.16±to 43.32. Below the age of 20 years, no other malignancies were found except ovarian cancer. Most of the cancer was diagnosed by histopathological examination. Cervical cancer patients were mostly multiparous (1700, 62.5%). About 67% cervical cancer patients received their first treatment at NICRH and remaining patients got their treatment started elsewhere. Most of the cervical cancer was squamous cell carcinoma (93%) and ovarian cancer was adenocarcinoma.

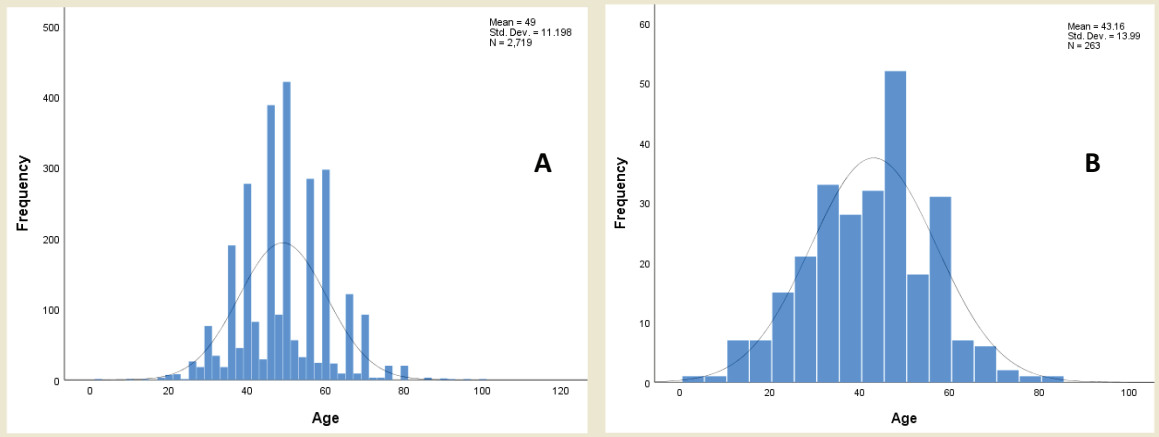

Fig.-1: *Age distribution of the patients A) Cervical cancer B) Ovarian cancer*

Table-I: *Cancer of female genital organ (2015-2017)*

Site	Frequency	Percentage
Cervix	2719	77.62
Uterus	212	6.05
Ovary	483	13.78
Vagina	65	1.85
Vulva	23	0.65
Placenta	01	0.02
Total	3503	100

Table II: *Morphology of cervical cancer (2015-2017)*

Morphology	Frequency	percentage
Sq cell ca	2526	92.90
Adenocarcinoma	174	6.40
Endometrioid	06	0.22
Other types	13	0.48
Total	2719	100.0

Table III: *Parity of Ca Cervix (2015-2017)*

Parity	Frequency	percentage
Grand Multipara	711	26.14
Multipara	1700	62.53
Primipara	182	6.69
Nullipara	126	4.64

Table IV: *Case referral*

Year	Prior treatment	New case
Cervical cancer		
2015	272	527
2016	239	622
2017	289	770
Ovarian cancer		
2015	26	31
2016	42	50
2017	65	49

Discussion

Significant contribution of female morbidity and mortality is attributed to gynaecological malignancies all over the world. In the present study cancer cervix was the commonest histologically confirmed gynaecological malignancy that constituted 77.19% of the cases. This finding was in line with that of an international study.[4] The next one is ovarian carcinoma followed by uterine carcinoma. However, vulval malignancy and vaginal malignancy had the least contribution (0.65% and 1.85% respectively). The nearly similar observations were found in a hospital-based study in Ghana which had reported cervical cancer was the commonest, constituting about 57.8% of gynaecological cancer followed by ovarian, endometrial and vulval carcinoma (25.3%, 7.4% and 2.2% respectively).[12] But studies from Pakistan have reported ovarian cancer to be more prevalent than other gynaecological cancers.[13] Majority of cancers presented between 4th & 6th decade of life with a peak incidence 5th decade. Endometrial and ovarian cancers were more common in the older age group while cervical cancer was more common in the pre and perimenopausal age group.[12] In the present study most common histological type of carcinoma cervix is squamous cell carcinoma (92.9%).[14] In our study cancer cervix was common among women with high parity (3-4). Similar results were found in study of Ellenson et al.[10] and Nkyekyer et al.[12] But one Nigerian study showed that cancer cervix occurred at grand multipara (5 and above).[15]

Of the ovarian malignancies, epithelial tumours were predominant followed by germ call tumours. Serous adenocarcinoma was the most common histological type of epithelial tumour. Efforts have been directed to early detection by devising different screening modalities like risk factor stratifications, serial transvaginal scans and tumour markers. It is suggested that screening should be offered to 50 years and above women considering them a high-risk group.

Conclusion:

The commonest genital tract malignancy is carcinoma cervix in developing countries which was also found in our study. The cause is early marriage, low socioeconomic condition, and lack of awareness of screening. It is sad that although the cervix is accessible, carcinoma cervix is detected late because of the ineffectiveness of existing surveillance and the illiteracy of women. Public awareness strategies should be devised by the government with a focus on screening and early reporting. Community education of women in the form of screening as well as early warning symptoms of malignancy is essential for the prevention and early

detection of malignancies. Even if cancer is not evident, a continuation of follow-up checking on a regular basis needs to be ensured.

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Original Article

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Bacteriological Profile and Antibiogram of Cancer Patients in NICRH

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Abstract:

Background: *Opportunistic bacterial infections remain serious morbidity and mortality among cancer patients. This study was conducted in the Microbiology department of NICRH to explore the bacteriological spectra of infections of various cancer patients with their susceptibility patterns.* ***Methods:*** *The study was done among cancer patients who attended NICRH from 01/07/2020 to 30/06/2021. Samples were collected from the diagnosed cancer patients who were advised by the clinicians to do the culture and susceptibility test of various samples. Then the culture and susceptibility reports were collected and analyzed in the microbiology department of NICRH.* ***Results:*** *A total of 282 samples were analyzed. Among them, 94 samples have shown positive cultures of which 47 (50%) were wound swabs, 41 (43.6 %) were urine, and the rest 6 (6.4 %) were blood samples. The predominated isolated organism was* E.coli *(76.6 %) followed by* Pseudomonas *(12.8%),* Staphylococcus *(9.6 %) and* Klebsiella *(1 %). Most of the* E.coli *strains showed the highest resistance to Aztreonam (ATM), Cefixime (CFM), Cefotaxime (CTX), Ceftriaxone (CRO), Nalidixic Acid (NA). Still, it was sensitive to Amikacin (AK), Linezolid (LNZ), Cephalexin (CL), Doxycycline (DO), and Gentamycin (CN).* E.coli *showed 100% resistance to Erythromycin (E).* Pseudomonas spp. *were sensitive to Amikacin (AK), Aztreonam (ATM), Ciprofloxacin (CIP), Gentamycin (CN), Piperacillin (PRL), and Polymyxin-B (PB). But* Pseudomonas *was 100% resistant to Carbenicillin (CAR), Cefotaxime (CTX), Ceftriaxone (CRO), Colistin (CL), Imipenem (IMP), and Meropenem (MEM).* ***Conclusions:*** *Gram-negative bacteria* E.coli showed the *highest resistance to ceftriaxone, Cefotaxime, Cefixime, and Nalidixic Acid, whereas it showed sensitivity to Amikacin, Doxycycline, and Polymyxin B.* Staphylococcus aureus*, Gram-positive coccus was sensitive to only Vancomycin and Linezolid but resistant to Erythromycin.* Pseudomonas *spp. was sensitive to Piperacillin and Polymyxin B but 100 % resistant to Carbenicillin.*

Key words: Bacteria, Antibiogram, Cancer patients, NICRH

Introduction:

Cancer patients are more vulnerable to bacterial infections due to the disease process concomitantly or subsequently in the causation of immunosuppression. Most patients undergoing chemotherapy may get opportunistic bacterial infections which remain a serious cause of morbidity, leading to disturbance in the treatment regimen, prolonged hospitalization, increased cost of health care, and reduced survival.[1] Though the mortality rates have fallen over the past years; bacterial infections remain a primary or associated cause of death.[2]

The management of the infections is based on the use of appropriate empirical antimicrobial therapy according to antibiotic susceptibility patterns, due to this, the relative incidence of Gram-negative bacterial infections has declined, but Gram-positive bacteria are more commonly seen. [3] As a result, nowadays, changes in the bacteriological profile of infections led to the emergence of multidrug-resistant (MDR) bacteria which are commonly encountered among immuno-compromised patients.[4] Despite many unusual pathogens infecting patients with underlying immunodeficiency, advanced knowledge of infectious etiology and appropriate antimicrobial agents can significantly improve the treatment and reduce mortality.[5]

To successfully prevent, identify and treat infections, sound knowledge of the ever-changing spectrum of infections is necessary. Management of bacterial infection is a major challenge in treating multi-drug resistant (MDR) bacteria.[6]

This study aims to evaluate the common types of bacterial infections in cancer patients attending the OPD of NICRH and the admitted patients and their susceptibility patterns. This will aid in improving treatment and prognosis and also reduce the cost of health care.

Aims and objectives: This study was done to monitor the types of bacterial infections seen in cancer patients undergoing anticancer treatment, and the associated bacterial pathogens with their antibiotic susceptibility patterns.

Materials and Methods:

a) Place and study period: The study was carried out in the Department of Microbiology of NICRH, Mohakhali, Dhaka-1212, for one year from 01/07/2020 to 30/06/2021.

b) Study population and inclusion criteria: A total of 282 clinically diagnosed cancer patients advised by the clinicians to do the culture and sensitivity test were included in the study. Those who were already on antibiotic treatment were excluded from the study.

c) Methodology: The samples received from suspected cases of infections were stained with Gram stain and then inoculated onto the blood agar, Mac Conkey agar (Hi-Media) media, and incubated aerobically at 37^0 C for 24 hours. Blood culture was done by Bact/ ALERT system (BIO Merieux, USA). Positive cultures were subcultured onto blood agar, Mac Conkey agar media, and incubated aerobically at 37^0 C for 24 hours. The bacterial isolates were identified through various chemical tests (fermentation reaction test in KIA media, motility test in MIU media, and citrate utilization test).[7] The bacterial isolates were tested for antimicrobial susceptibility by agar disk diffusion method against different antimicrobial agents like Amoxicillin (AML), Amikacin (AK), Azithromycin (AZM), Aztreonam (ATM), Carbenicillin (CAR), Cephalexin (CL), Cefixime (CFM), Cefotaxime (CTX), Ceftriaxone (CRO), Ciprofloxacin (CIP), Colistin (CO), Doxycycline (DO), Erythromycin (E), Gentamycin (CN), Imipenem (IMP), Levofloxacin (LEV), Linezolid (LNZ), Meropenem (MEM), Netilmycin (NET), Nitrofurantoin (F), Nalidixic acid (NA), Piperacillin (PRL), Polymyxin B (PB), Cotrimoxazole (STX), Vancomycin (VAN), etc. [8] The diameter of complete zone of inhibition around each disc was measured in mm. The antimicrobial susceptibility testing of the isolates was performed according to the clinical and laboratory standard institute (CLSI) guidelines.

d) Statistical analysis: The data were entered into an MS Excel worksheet and analyzed using SPSS for Windows software version 25. Qualitative data were presented in the form of graphs and frequency tables.

Results:

In this study, out of 282 diagnosed cancer patients, 152 (54%) attended the OPD, and 130 (46%) were admitted patients. The age and sex distribution are shown in Tables I and II, respectively. The patients' age ranged from 1-90 years. The maximum cases belonged to the age group 41-50 (22.7%). The female patients were predominant in this study, and the male: female ratio was 0.6:1.

Table I: *Distribution of age*

Age (in years)	Frequency (n)	Percent (%)
1-10	17	6.0
11-20	33	11.7
21-30	32	11.3
31-40	61	21.6
41-50	64	22.7
51-60	47	16.7
61-70	20	7.1
71-80	07	2.5
81-90	01	0.4
Total	282	100

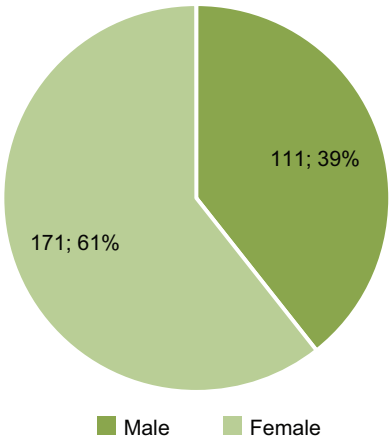

Fig.-1: *Distribution of Gender*

Among 282 cases, 188 (66%) patients showed no growth in their samples, whereas 94 (34%) cases were culture-positive, as shown in Table III. Among them, 41 (44%) were culture-positive urine samples, 47 (50%) were wound swab samples, and the rest 6 (6%) were blood samples (Table III).

Table II : *Growth/ no growth*

Organism growth	Frequency (n)	Percent (%)
No growth	188	66
Growth	94	34
Total	282	100

Table III: *Types of culture-positive samples*

Samples	Frequency (n)	Percent (%)
Urine	41	44
Wound swab	47	50
Blood	06	06
Total	94	100

The aetiological agents associated with infections are shown in Table V. The most common isolate related to urinary tract infection (UTI) was *E.Coli* followed by *Staphylococcus aureus*. *E.Coli* is also associated with wound infection along with *Pseudomonas spp*. and *Staphylococcus*. Blood cultures have shown *E.Coli, Pseudomonas,* and *Staphylococcus* positive cases in 3 (three), 1 (one), and 2 (two) samples, respectively.

Table V: *Types of isolated organisms*

Organisms	Frequency (n)	Percent (%)
E.coli	72	76.6
Pseudomonas spp.	12	12.8
Staphylococcus	09	9.6
Klebsiella spp.	01	1.0
Total	94	100

The antibiogram showed *E.coli* was mainly sensitive to Amikacin, Doxycycline, Gentamycin, and Meropenem and resistant to Cefixime, Aztreonam, Cefotaxime, Ceftriaxone, Ciprofloxacin, Imipenem, Nalidixic acid, etc. *Pseudomonas* spp. was 100% resistant to Amoxicillin, Carbenicillin, Cefotaxime, Ceftriaxone, Colistin, and Imipenem but was sensitive to Amikacin, Aztreonam, Ciprofloxacin, Gentamycin, Netilmicin, Piperacillin; Polymyxin B. Staphylococcus was sensitive to Cephalexin, Doxycycline, Gentamycin, Netilmicin, Polymyxin B and Vancomycin but was resistant to Amoxicillin, Cefotaxime, Ciprofloxacin, Colistin, Erythromycin, Meropenem, Nalidixic Acid, and Piperacillin.

Discussion:

Infections are still a cause of substantial morbidity and mortality in cancer patients. The important infections are urinary tract infection (UTI), wound infection, bloodstream infection, pneumonia, sepsis, influenza, etc. In our study, out of 282 patients, 94 (34 %) samples are culture-positive, and 188 (66 %) are culture-negative. Among 94 culture-positive samples, 85 (90%) show Gram-negative and 9 (10 %) are gram-positive bacteria.

In most studies from developed countries, around 70 % of infections are caused by Gram-positive bacteria. On the contrary, most studies conducted in developing countries have recorded that most infections were caused by Gram-negative organisms. The explanation for this fact may be attributed to less usage of prophylactic antimicrobial regimens in neutropenic patients in different setups. Gram-negative bacteria have predominated as a major cause of infections in cancer patients in the last 20 years, similar to our study. [9] Among Gram-negative bacteria, *E.coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* have been increasingly associated with cancer patients. Nowadays, inadequate empirical antimicrobial therapy exposes cancer patients

to an increased risk of adverse outcomes, especially in neutropenic bacteremic patients suffering from MDR infections. [10] In the study of Eleni Isidore *et al.*, 14% of the study group had previous MDR colonization, which possibly contributed to an increased risk of MDR infection.

In the study of Kumar *et al*, in Mumbai, the overall rank order of the most common pathogens was *Pseudomonas spp*. (26.2 %) > *Staph. aureus* (11.44 %) > *E.coli* (11.34 %) > *Klebsiella spp.* (10.59%). This is not similar to our study, where the rank order was *E.coli* (76.6 %) > *Pseudomonas spp.* (12.8 %) > *Staph. aureus* (9.5 %) > *Klebsiella spp.* (1.1 %). They found Gram-negative accounted for 66.96 % of the isolates, which is similar to our findings (90 %). [11]

In our study, among 282 cancer patients, 94 patients succumbed to infections, of which 71 (84%) were cancer patients with MDR *E.coli*. MDR bacterial infections were thus significantly associated with mortality in cancer patients.[12]

Limitation of the study: This study was conducted in a single institution and could not reveal the epidemiology of other centers.

Conclusion:

Infections remain a significant cause of mortality among cancer patients, despite improved management. Implementing strict infection control practices and empirical antimicrobial therapy can improve this dreaded situation. In developing countries, the broad spectrum of empirical therapy must focus more on treating Gram-negative infections. It increases the cost of patient care and leads to the selection of MDR organisms, as seen abundantly in this study, as well as many others. The prospective studies on antibiotic sensitivity patterns in hospitals will help to formulate appropriate guidelines and therapeutic studies. The increasing development of resistance to existing antimicrobials necessitates a dire need to develop novel agents faster than the development of resistance. It is crucial to restrict the use of antibiotics in all clinical practices. Using narrow-spectrum antibiotics based on culture reports whenever possible. This may go a long way in improving the situation of patients with life-threatening infections, especially those immunocompromised.

Summary: Bacterial infections among cancer patients are one of the major challenges. It leads to suboptimal delivery of chemotherapy, causing poor treatment outcomes, adds to the cost of management, and contributes to increase morbidity. Resistant organisms have emerged owing to selective antimicrobial pressure, which further complicates the problems. To successfully prevent, identify and treat infections, knowledge of the changing epidemiology of infection is essential. In this study, we detect the type of infection seen in the diagnosed cancer patients undergoing anticancer treatments, the associated bacterial pathogens, and their antibiotic susceptibility patterns.

Study implications: This study helps to achieve a precise knowledge of the common types of infections seen in cancer patients undergoing various forms of therapy, the associated bacterial isolates, and their susceptibility. This will aid in formulating a personalized and cost-effective treatment, improving prognosis and ensuring the appropriate use of antibiotics.

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Case Report

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Krukenberg Tumour: Our Experience at NICRH

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Abstract

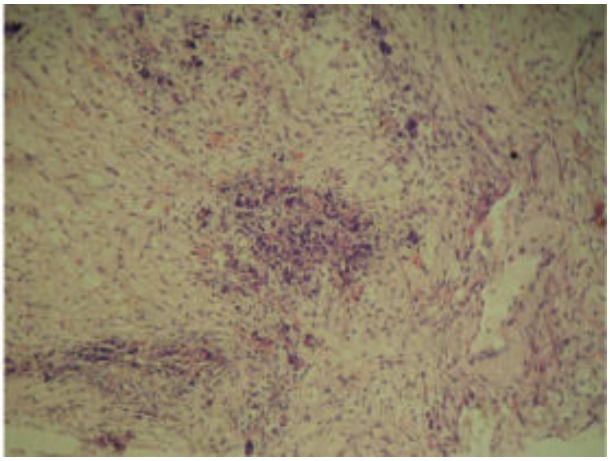
Krukenberg is an uncommon metastatic tumour of the ovary with transcoelomic spread and accounts for 1-2 % of all ovarian tumours. The stomach is the most common primary site, but other organs can serve as primary sites. Ovarian metastases originating from the stomach (primarily defined as Kruckenberg tumours) are usually seen in female patients with gastric cancer. It is considered a late-stage disease, and the prognosis is still dreadful. Herein, we report a rare case of a 45-year-old woman who had a history of total gastrectomy (biopsy showed adenocarcinoma) and presented with bilateral ovarian masses. A total hysterectomy with bilateral salpingo-oophorectomy was performed. Histology showed signet ring tumour cells within a cellular ovarian stroma. Ovarian metastasectomy might help prolong the survival time of some patients with Krukenberg tumours originating from the stomach.

Keywords: *Krukenberg tumour, metastatic tumour, Bangladesh*

Introduction

Krukenberg tumour, an uncommon metastatic tumour of the ovary, originates in the stomach in most cases.[1] In 1896, Friedrich Krukenberg (1871–1946), a German gynaecologist and pathologist, described a new type of primary ovarian neoplasm. The true metastatic nature of this lesion was established 6 years later.[2] Krukenberg tumour is a metastatic signet ring cell adenocarcinoma of the ovary.[1] Metastasis usually arises from the upper parts of the gastrointestinal tract [stomach (70%), pancreas, and biliary tract], breast and sometimes other organs like kidney, lungs, thyroid and endometrium.[3] It is a rare tumor and accounts for 1-2% of all ovarian tumors.[4] 80% cases of Krukenberg tumors are bilateral and consistent with its metastatic nature.[5] It may mimic other metastatic or primary ovarian tumors and complicate diagnosis.[6]

A lady aged 45 years para 4+0 had a history of lower radical Gastrectomy. Histopathology report showed adenocarcinoma of stomach grade II with lymphnode metastasis. She took six cycles of chemotherapy with paclitaxel and carboplatin. One year after the radical gastrectomy, during her follow-up period, she presented with pain in the abdomen, distension and loss of appetite and a mass in the lower abdomen. On general examination, no abnormality was detected. On local



examination, there was a mass solid in nature, non-tender, restricted mobility and lobulated surface, occupying the right iliac, hypogastric, left iliac and partly left lumber region. On bimanual examination, the cervix was found apparently healthy. A bilateral solid mass was palpated through the anterior and both lateral fornices, which were separated from the uterus. USG of the whole abdomen reveals a large complex mass having both cystic and solid components. Ovaries could not be separately identified. Cul de sac was free from fluid. FNAC of the abdominal mass shows the presence of malignant cells suggestive of metastatic adenocarcinoma. Chest X-Ray was normal.

Following laparotomy, peritoneal fluid was taken for cytological study. The undersurface of the diaphragm, liver, spleen and kidney were palpated for metastatic deposit. There were two large ovarian tumours on the right side. The larger one measure about 13x10x8 cm, and the smaller one measures 11x7x7 cm. The masses were lobulated with a smooth surface. One mass was densely adherent to the gut and omentum, and anterior and lateral parietal peritoneum Adhesiolysis was done. Another mass was on the left side, measuring about 9x7x5 cm, which was free of adhesion. Laparotomy followed by Total Abdominal Hysterectomy with bilateral salpingo-oophorectomy was done.

On gross examination, both ovaries were asymmetrically enlarged, and the right ovary measured 8X8 cm, and the left ovary measured 6X8 cm, respectively. Externally, both ovaries showed irregular, nodular, with a bosselated appearance.

The cut section was lobulated, greyish-white in colour, with cystic areas.

H & E stained sections show both hypercellular and hypocellular areas having fibroblastic proliferation. Serial sections showed signet ring tumour cells within a cellular ovarian stroma. The tumour cells were arranged singly or in nests with eccentric nuclei and large, pale and vacuolated cytoplasm filled with mucin.

Fibroblasts are arranged in fascicles, whorles with interspersed vessels and oedema at places. There are malignant epithelial cells with oval nuclei, prominent nucleoli & well-defined cytoplasm showing a high degree of pleomorphism and increased N/C ratio. The cells are found to form acinus structures with intracellular mucin production to form a signet ring appearance. There are considerable numbers of atypical mitosis in the whole section.

She started chemotherapy but unfortunately, before completing the first cycle, she died.

Conclusion:

Ovarian metastases originating from the stomach (primarily defined as Krukenberg tumour), are usually seen in female patients with gastric cancer.[7,8] It is considered a late-stage disease, and the prognosis is still abysmal.[9] Until now, optimal treatment has not been established, and it is still uncertain whether surgical resection of ovarian metastases could improve the outcome.

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Review Article

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Management of Retroperitoneal Sarcoma: An Update

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Abstract

Retroperitoneal sarcomas (RPS) are extremely rare malignancy account for only 0.1 to 0.2% of all malignancy. It often reaches massive size before detection. The mainstay of treatment for RPS is surgical resection and complete resection is the only chance for potential cure. The management of RPS can be challenging and in individual cases, radiation and systemic therapy may be beneficial. In the future, precision medicine with next generation sequencing technology will be expected among the diverse and potential future treatment for retroperitoneal sarcoma.

Key words: *Retroperitoneal sarcoma, Liposarcoma, Leiomyosarcoma*

Introduction

Retroperitoneal soft tissue sarcomas (RPS) are rare tumours that account for approximately 12-15% of all soft tissue sarcomas, with a mean incidence of 2.7 per million. RPS are frequently incidental findings in the work-up for non-related symptoms or diseases. They can grow to an extremely large size in the retroperitoneum before symptoms or signs of abdominal pain, back pain, bowel obstruction or a palpable abdominal mass develop.[1]

RPS account for just 0.1–0.2% of all malignancies. Retroperitoneal sarcoma is the most common malignant RPT, but primary and metastatic germ cell tumors, metastasis of any epithelial tumor, and the other malignant tumors also occur in the retroperitoneal cavity.[2] In Europe, the incidence of soft tissue sarcoma is 4–5 per 100 000 a year. In Japan, 1529 soft tissue sarcoma cases involving the limbs and trunk were diagnosed in 2015. It was estimated that approximately 230–300 cases were RPS, according to the Musculoskeletal Tumor Committee of the Japanese Orthopedic Association.[3]

Most RPS occur sporadically. Some are associated with genetic disorders. Hereditary diseases associated with

RPS include Li–Fraumeni syndrome, neurofibromatosis-1, retinoblastoma, familial adenomatous polyposis, Werner syndrome, basal cell nevus syndrome and tuberous sclerosis complex. The occurrence of RPS within 3 years of radiation therapy has also been reported.[2]

The histological type of RPS

Although >70 histological types of sarcomas have been identified, liposarcoma and leiomyosarcoma account for most RPS. In the National Cancer Database cohort of retroperitoneal sarcomas (n = 6857), the prevalence of liposarcoma, leiomyosarcoma, undifferentiated sarcoma (not specified), malignant peripheral nerve sheath tumour, solitary fibrous tumour, fibrosarcoma, angiosarcoma, synovial sarcoma and rhabdomyosarcoma was 56.3%, 27.2%, 11.3%, 1.3%, 1.1%, 1.0%, 0.6%, 0.5% and 0.5%, respectively.[2] Many histology types in soft tissue sarcoma are usually found in the extremities and trunk. Liposarcoma and leiomyosarcoma often occur in the retroperitoneum and the pelvis. The histological RPS types after receiving radiation therapy associated with the other malignant tumours were mostly undifferentiated pleomorphic sarcoma2.

Diagnosis

The retroperitoneum offers an environment where sarcomas can grow to a large size before becoming symptomatic. Frequently retroperitoneal sarcomas are incidentally diagnosed as part of a workup for other problems. Patients typically present with an abdominal mass. Often, patients have no other complaints, as constitutional symptoms are uncommon. If symptoms are present, this is typically related to the tumour invading a regional structure or causing mass effect to surrounding organs that can cause pain, lower extremity swelling, loss of appetite, or weight loss.

Although the size of the tumour and the presence or absence of fatty components can be distinguished using CT and/or MRI, a case of dedifferentiated liposarcoma with a lower fat component cannot be distinguished correctly.[4] In this case, needle biopsy is becoming more useful for definitive diagnosis. In rhabdomyosarcoma, which is more common in childhood, and Ewing's sarcoma, which is more sensitive to chemotherapy and radiation therapy, chemotherapy has priority over surgery. Needle biopsy helps to perform histological typing and grading.

MRI can assist in doubt on muscles, bones, foramina, and neurovascular structures involvement. It is essential to assess the pelvic masses' extent and evaluate the indication for radiotherapy and its treatment volume. If the surgery involves the removal of a kidney, a functional examination of the contralateral could be considered.

It is very difficult to correctly determine the histological type given the 70 different histology types of RPS. In determining the histological type, the diagnostic accuracy can be improved by using a genomic method investigating some mutations in individual sarcoma-specific genes, specific miRNA differentiation and translocation confirmation using fluorescence in situ hybridization, regardless of the morphological diagnosis. Over recent years, the CT-guided biopsy approach through the retroperitoneum was found to have a higher value than ultrasound-guided biopsy.[5]

TNM staging in retroperitoneal sarcomas

The AJCC/TNM classified by primary tumour (T), regional lymph node (N), distant metastasis (M) and histological grade (G) was adopted and updated to the 8th edition in 2017. In the 8th edition, tumour size was classified into four groups as follows: (i) d"5 cm; (ii) >5 cm and d"10 cm; (iii) >10 cm and d"15 cm; and (iv) >15 cm. The depth of the primary soft-tissue tumor (superficial or deep from the superficial fascia) had been eliminated and excluded as a staging factor in the 8th edition.[6]

Soft tissue sarcoma has different stages depending on the primary site. For example, TanyN1M0 is classified as stage 4 when it is found in the trunk and extremity, but as stage 3B when found in the retroperitoneal cavity.

Treatment

Surgical resection

The most critical component of the treatment of RPS remains the surgical excision, and the best chance for cure is at the time of primary surgery. Surgery should achieve macroscopically complete excision of the tumour (R0 or R1), minimizing marginality, ideally through an en bloc resection of all potentially involved structures as determined by careful preoperative imaging combined with intraoperative findings.[7]

Contraindications to primary resection are believed to be bilateral renal involvement; encasement of the superior mesenteric artery, celiac axis, porta hepatis; and spinal cord involvement.

Resection of RPS requires technical expertise in multiple sites throughout the abdominal and pelvic cavity, including handling large vessels. More than single organ/site expertise is required. The ability to orchestrate a team of complementary surgical experts is critical to the successful management of RPS patients. To minimize the risk of intraoperative and perioperative morbidity, RPS resection should be undertaken by surgical teams with expertise in specific aspects of the anatomy of the retroperitoneal space—for example, expertise in retroperitoneal autonomic and somatic nerves, the lymphatic system, paravertebral vessels, and organs of the gastrointestinal tract. Required expertise also includes experience with additional procedures, such as full-thickness thoracoabdominal wall resection and reconstruction, diaphragmatic resection and reconstruction, major vascular resection and reconstruction, and bone resection. Surgical teams with these abilities, which may accrue from prior participation in multidisciplinary surgical teams, can achieve macroscopically complete tumour resection in most patients.

In RPS cases wherein local control is possible, radical combined aggressive surgical excision of adjacent organs can achieve R0/R1 resection. In contrast, for RPS, such as leiomyosarcoma, which often recurs with distant metastases, even if multiple adjacent organs are resected together at surgery, the survival rate and recurrence risk cannot improve. Multimodal therapy, including radiation therapy and chemotherapy, is required for these histologies.[8]

Multiple organ resection increases the risk of postoperative complications. Mortality rate increases with the simultaneous resection of three or more organs in the perioperative period. However, complications resulting from surgical resection did not affect the OS for RPS, because it showed a slight difference statistically. Most hospitals that carry out simultaneous excision of many organs with RPS resection are centralized hospitals. Depending on the organs resected during combined resection, the complication risk differs. It is low when the intestinal tract and kidneys are involved. Meanwhile, it is high when the pancreas and duodenum are involved.[9]

Radiation therapy

The overall benefit of radiotherapy for retroperitoneal sarcoma has yet to be established. However, concern remains about the increased risk of treatment-related toxicity to highly radiosensitive visceral structures due to their rapidly proliferating mucosa and rich blood supply. The relatively low rate of radiation tolerance for surrounding normal tissues (liver, kidney, gastrointestinal tract, spinal cord) predisposes patients to risks of intestinal perforation, peritonitis, and peripheral neuropathy.[10]

Preoperative radiotherapy is currently being investigated in an accruing, prospective, randomized, multicenter trial (NCT01344018). This trial investigates the potential for external beam radiotherapy (EBRT) to reduce local and regional failure. Proponents of preoperative radiation cite the potential benefits of using lower doses while the tumor displaces radiosensitive viscera outside the radiation field. Proponents also claim that gross tumor volume can be more adequately defined, allowing for more accurate preoperative treatment planning.[11]

The use of postoperative EBRT has been studied but abandoned mainly due to its toxic effects on the remaining organs within the tissue bed after resection, with no apparent improvement in survival. Another concern with postoperative radiation suggests the difficulty in defining a precise area of the tumor bed to apply EBRT.[3]

Moffitt Cancer Center favors preoperative EBRT for intermediate- to high-grade tumors, especially in more radiosensitive tumors, such as extraosseous Ewing sarcoma/primitive neuroectodermal tumors. The more common subtypes, such as well-differentiated liposarcoma and leiomyosarcoma, are generally unresponsive to radiation.[11]

Recently, in addition to surgery for RPS, the effectiveness of perioperative radiation therapy has become interesting. In a matched case-control analysis they were using data from the nationwide clinical oncology database jointly administered by the American Cancer Society and the American College of Surgeons, the treatment group with perioperative radiation therapy before surgery (n = 563, HR 0.70, 95% CI 0.59–0.82; P <

0.001) or after surgery (n = 2215, HR 0.78, 95% CI 0.71–0.85; P < 0.001) had better OS than the surgery alone treatment group (n = 6290). Therefore, to verify the efficacy of perioperative radiotherapy in Europe, a multicenter randomized controlled trial was compared between the group with preoperative radiotherapy followed by surgery and resection alone for primary RPS (STRASS trial: EORTC 62092-22092; NCT01344018). However, the study results reported in 2019 did not show the usefulness of preoperative radiotherapy. Other clinical trials with radiation therapy are ongoing.[12]

Systematic drug therapy

The decision of preoperative or postoperative chemotherapy must be made by an experienced medical oncologist and on an individualized patient basis. In 1993, results were published on a 3-armed phase III clinical trial in patients with STS evaluating regression rates, toxicity, and OS using doxorubicin alone, ifosfamide and doxorubicin, and mitomycin with doxorubicin plus cisplatin. In this study, 279 patients were enrolled and 262 patients were randomized; cohort A received doxorubicin 80 mg/m^2, cohort B received ifosfamide 7.5 g/m^2 plus doxorubicin 60 mg/m^2, and cohort C received mitomycin 8 mg/m^2 with doxorubicin 40 mg/m^2 plus cisplatin 60 mg/m^2. In cohort A, receiving doxorubicin alone, there was an objective regression in 20% of patients; there was a 34% objective regression in cohort B, receiving doxorubicin and ifosfamide, and a 32% objective regression in cohort C, receiving mitomycin with doxorubicin plus cisplatin. While cohort B had a higher response rate, this group also experienced more toxicities and myelosuppression than cohort A or C. There was also no significant improvement in OS.[13]

Following this trial, there was a randomized clinical trial looking at adjuvant epirubicin with or without ifosfamide for adults with STS. Following a curative surgery, patients were randomized to chemotherapy or no chemotherapy with radiation being at the investigator's discretion. In the chemotherapy cohort, initially, 26 patients received epirubicin 75 mg/m^2 alone once every 21 days. After 1991, the chemotherapy cohort was changed so that these patients received epirubicin 25 mg/m^2 on days 1-3 and ifosfamide 1,200 mg/m^2 on days 1-5 every 4 weeks. Unfortunately, this trial closed prematurely due to poor accrual. The results did indicate a statistically significant improvement in the 5-year DFS of patients who received adjuvant chemotherapy (69%) vs. those who received no chemotherapy (44%) as well as the OS, 72% with patients who received adjuvant chemotherapy vs. 47% without.[14]

A second European trial examining adjuvant chemotherapy was performed using the two most active chemotherapy agents with a high-dose-intensive regimen. Patients 18-65 years of age with grade 3-4 spindle-cell sarcomas were randomized to either receive epirubicin 60 mg/m^2 days 1 and 2 and ifosfamide 1.8 gm/m^2 days 1-5 or the control arm which received no chemotherapy. There were 104 patients enrolled in the trial, 53 patients were in the chemotherapy arm, and 51 patients were randomized to the control arm. The accrual of the trial was discontinued prematurely after an interim analysis of DFS revealed a significant benefit for the chemotherapy arm. The overall DFS was 48 months in the chemotherapy cohort with a 41% relative risk reduction in disease relapse and an absolute improvement of 27% at two years and 13% at four years. The control arm exhibited only 16 months overall DFS.[15]

Therefore, data from 2 phase III clinical trials were pooled by the EORTC-Soft Tissue Bone Sarcoma Group for patients with localized high-grade soft tissue sarcomas evaluating relapse-free survival and OS in patients who received adjuvant chemotherapy. The first study analyzed was EORTC 62771, which consisted of 468 patients using doxorubicin 50 mg/m^2 on day 1, dacarbazine 400 mg/m^2 given on days 1-3, cyclophosphamide 500 mg/m^2 on day one and vincristine 1.5 mg/m^2 on day one (CYVADIC); this regimen was given every four weeks for eight cycles. The second trial analyzed was EORTC 62,931 which consisted of 351 patients given doxorubicin 75 mg/m^2 and ifosfamide 5 g/m^2 on day one given every 21 days for five cycles. The data compared relapse-free survival and OS in patients who received chemotherapy vs. observation alone following complete resection. A total of 819 patients were enrolled and followed for a mean of 8.2 years. What was observed was that although adjuvant chemotherapy improved relapse-free survival (hazard ratio [HR] 0.74), there was no improvement in OS. Subgroup analysis revealed that patients with marginal (R1) resections did seem to have an OS benefit with adjuvant chemotherapy (HR 0.64) while patients with R0 resections had no benefit (HR 1.07).[16] However,

it must be stressed that adjuvant chemotherapy is not used as a strategy to compensate for inadequate oncologic surgery. These results validate the importance of having the proper surgery completed with stringent follow-up regardless of the therapeutic regimen prescribed.

The Italian Sarcoma Group in collaboration with the Spanish Sarcoma Group, followed their high-dose adjuvant trial with a phase III randomized clinical trial for localized, high-risk, soft tissue sarcoma using the epirubicin-based chemotherapy with ifosfamide. There were 321 patients that were randomized into two arms; one of the arms received three neoadjuvant cycles of epirubicin 120 mg/m2 plus ifosfamide 9 g/m^2 and in the other arm, patients received the same three cycles of neoadjuvant chemotherapy with two additional cycles postoperatively. The results from this trial revealed that five cycles were not superior to 3 cycles in terms of overall and progression-free survival, and the treatment group who received five cycles experienced more adverse reactions.[17]

After the data resulted from the Italian Sarcoma Group and Spanish Sarcoma Group's phase III trial evaluating the benefit of three vs. five cycles of epirubicin and ifosfamide, it was suggested that a histotype-tailored chemotherapy regimen might be superior to the standard of care, epirubicin, and ifosfamide5.

Salvage systematic therapy after first-line was developed as a life-prolonging treatment.

In 2010, three new drugs for soft tissue sarcoma were approved based on the results of phase 3 trials, but the histological subtypes of the patients enrolled in the trials of each drug differed.

Pazopanib was approved in sarcomas in the PALLET (Pazopanib Versus Placebo in Patients with Soft-Tissue Sarcoma Whose Disease Has Progressed During or Following Prior Therapy; NCT00753688) trial, which excluded gastrointestinal stromal tumors and adipocytic sarcomas. In the PALLET trial, pazopanib yielded a better prognosis compared with the placebo (HR 0.31, 95% CI 0.24–0.40; P < 0.0001). The study cohort excluded liposarcoma, and thus the efficacy of pazopanib against liposarcoma has not been confirmed. The use of trabectedin compared with dacarbazine as a control drug improved PFS in leiomyosarcoma and liposarcoma after the failure of conventional chemotherapy (HR 0.55, 95% CI 0.44–0.70; $p < 0.001$; NCT01343277). Eribulin, compared with dacarbazine as a standard treatment, did not modify PFS, but improved OS (HR 0.77, 95% CI 0.62–0.95; $p = 0.0169$; NCT01327885).[3]

Many prospective trials using immune checkpoint inhibitors alone or combination therapy with chemotherapy, molecular target agents and so on are ongoing.

In recent years, molecular profiling has been used to select eligible patients for chemotherapy. The expression of CINSARC is evaluated in RPS patients. CINSARC is composed of genes involved in genomic instability, and this system acts as a powerful tool to identify tumors with metastatic potential. Currently, a phase 3 clinical trial is underway for the validation of the efficacy of preoperative chemotherapy for soft tissue sarcoma highly expressed by CINSARC.[17]

Using NGS technology, some studies on the method of diagnosis for sarcoma, confirmation of heterogeneity, validation of biomarker, validation of prognostic factors, drug sensitivity, and resistance to drug therapy are also being carried out. However, applying the findings clinically to soft tissue sarcoma with >70 histological types is still difficult. In recent years, NGS identified an LMNA-NTRK1 fusion protein. This was suspected to be a fusion driver requiring the clinical use of an NTRK inhibitor.[18]

Conclusion

For RPS, survival improvement and locoregional recurrence prevention can be undertaken by surgery to secure negative margins with wide and combined resection of some adjacent organs and cooperation with a trained medical team comprising radiologists, pathologists, and medical oncologists in centralized hospitals. Some clinical trials are in progress to further improve treatment results by adding preoperative chemotherapy and radiation therapy based on histological confirmation using a correct needle biopsy. In the future, precision medicine with NGS technology will be expected among the diverse and potential future treatments for RPS.

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