Asian Pacific
Journal of
Cancer Care

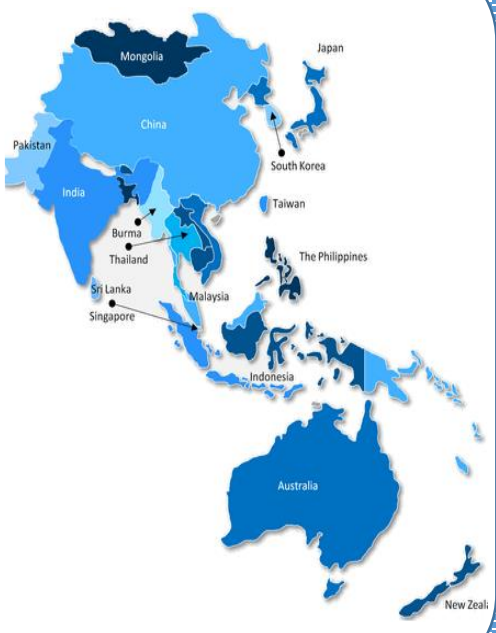
ISSN:2588-3682

An official publication of
Asian Pacific Organization for Cancer Prevention
(APOCP)
Since 2000

Volume 5, N2, 2020

Highlights of the issue

- **Epidemiology, Pattern of Recurrence and Survival in Triple-negative Breast Cancer. By Dharmendra Singh, et. al.**
- **The Role of 18F-FDG-PET/CT Scan in the Management of Multiple Myeloma. By Shirin Haghighat.**



CONTENTS

APJCC, Volume 5, No 2, 2020

DOI:10.31557/APJCC.2020.5.2.67

SHORT COMMUNICATION

Some Facts about Cancer in Karbala Province of Iraq, 2012-2020

Ahmed Mjali, Bushra Najeh Hasan Al Baroodi

Department of Hematology /Oncology, Al- Hussein Medical City, Karbala, Iraq.

Asian Pac J Cancer Care, **5 (2)**, 67-69

Submission Date: 02/17/2020 Acceptance Date: 05/02/2020

In 2018, more than 18 million new cases of cancer occurred around the world [1]. In Iraq there are over 31,500 cases of cancer between 2017 & 2018 making it one of the country's leading causes of death, contributing to an estimated 11% of total deaths [2]. Some experts argue that the leading cause behind cancer in Iraq is radioactive and environmental pollution due to the contamination of water, air and soil with carcinogens such as petroleum compounds [3-4]. Here we investigated cancer distribution in Al-Hussein cancer center in Karbala province of Iraq from 2012 to 2020.This center was established in November 2011 with oncology & hematology wards while health authorities in Karbala are planning for establishing radiotherapy department in future. This centre covers not only Karbala population but other patients from middle Euphrates region in Iraq are referred to this center for solid& hematological malignancy treatment [5]. There were 7468 cases were registered, male were 3117 patients (41.74%) and female were 4351 patients (58.26%), with (male to female ratio = 0.71:1). Female predominant may be explained by that our center is a referral center and many certain cancer like breast cancer refer to this center making the number of female more than male. People above 40 years old represent the majority of patients, presenting about 72.90% of cases. While those ≤ 20 years presenting about 11.40% (Table 1).

In general regardless of sex, breast cancer was the most common cancer registered in our center presenting about (24.49%), followed by lymphoma (8.90%), urinary bladder (7.53%), lung (7.36%), leukemia (6.93%), colorectal (6.42%), brain (5.16%), ovarian (3.02%), soft tissue sarcoma (2.97%) and prostate (2.97%) as shown in (Figure 1).

Top ten cancer type in males were urinary bladder (13.21%), lung (11.22%), lymphoma (10.60%), leukemia (9.23%), colorectal (8.40%), prostate (7.12%), head and neck (4.30%), soft tissue (3.91%), pancreas (3.68%) and brain (3.50%) as shown in (Figure 2) and (Table 2).

While the top ten cancer in females were breast (41.50%), lymphoma (7.70%), leukemia (5.30%), ovarian (5.20%), colorectal (5%), lung (4.60%), uterine & cervical (4.30%), urinary bladder (3.50%), thyroid cancer (2.70%) and soft tissue sarcoma (2.30%) as shown in (Figure 3) and (Table 2).

Table 1. Incidence Rate of Cancer According to Patients' Age

	Gender	
	Male n (%)	Female n (%)
0-10	253 (8.12)	277 (6.37)
11-20	164 (5.26)	157 (3.61)
21-30	168 (5.39)	246 (5.65)
31-40	238 (7.63)	521 (11.97)
41-50	425 (13.63)	1060 (24.36)
51-60	575 (18.45)	956 (21.97)
61-70	772 (24.77)	799 (18.36)
71-80	430 (13.80)	269 (6.18)
81-90	85 (2.73)	60 (1.38)
91-100	7 (0.22)	6 (0.15)

The number of cancer cases that registered in 2012 were 483 cases, while in 2019 more than 1200 cases were registered (Figure 4). Increase in cancer patients was steady increase not sharp increase this due to natural growing of population, increase awareness of disease and improving in diagnosis & registration. Our study may help to provide basic information to investigate epidemiological cancer characteristics, to assess progress in recent years and to develop future cancer treatment strategies.

Conflicts of interest

There are no conflicts of interest.

Corresponding Author:
Dr. Ahmed Mjali
Department of Hematology /Oncology, Al- Hussein Medical City, Karbala, Iraq.
Email: ahmedmajly@yahoo.com

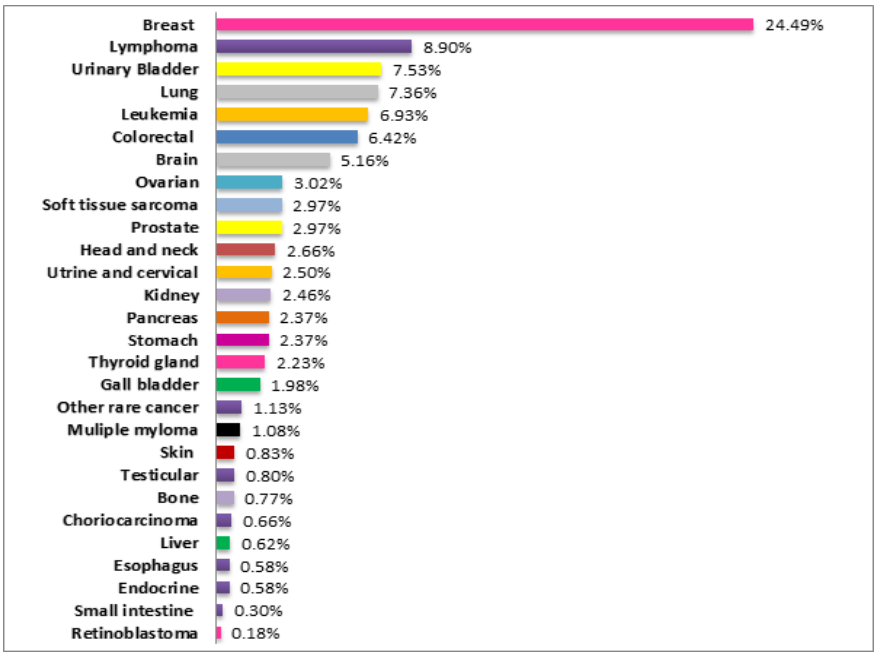


Figure 1. Incidence Rate of Cancer Types Regardless of Sex

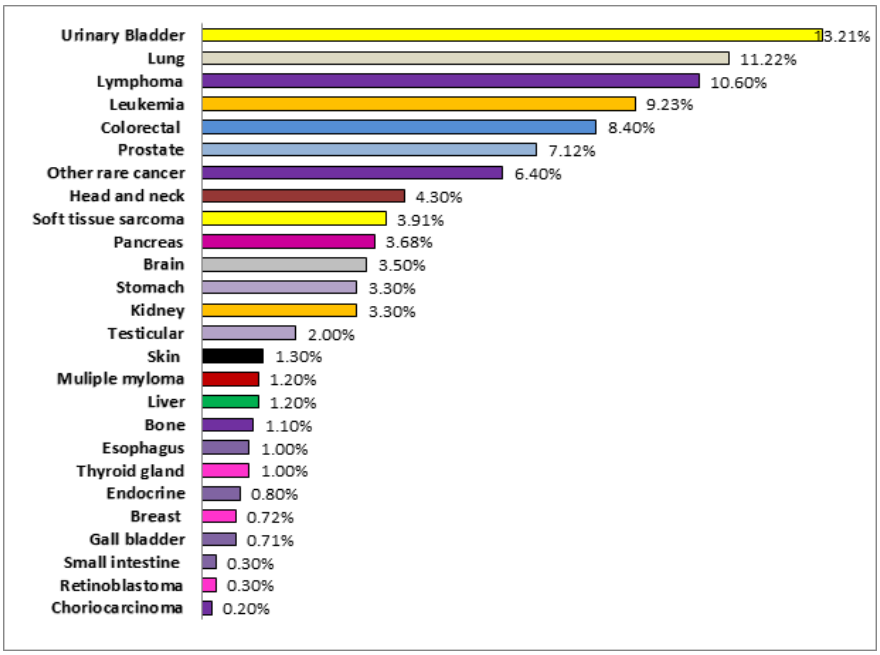


Figure 2. Incidence Rate of Cancer Types in Male

Table 2. Top Ten Cancer in Male and Female

	Male n (%)	Female n (%)
1	Urinary bladder 411 (13.21)	Breast 1806 (41.50)
2	Lung 350 (11.22)	Lymphoma 335 (7.70)
3	Lymphoma 330 (10.60)	Leukemia 231 (5.30)
4	Leukemia 287 (9.23)	Ovarian 226 (5.20)
5	Colorectal 262 (8.40)	Colorectal 218 (5)
6	Prostate 222 (7.12)	Lung 200 (4.60)
7	Head and neck 134 (4.30)	Uterine & cervical 187 (4.30)
8	Soft tissue 122 (3.91)	Urinary bladder 152 (3.50)
9	Pancreas 115 (3.68)	Thyroid cancer 117 (2.70)
10	Brain 110 (3.50)	Soft tissue sarcoma 100 (2.30)
11	Other 774 (24.83)	Other 779 (17.90)
	Total 3117 (100)	Total 4351 (100)

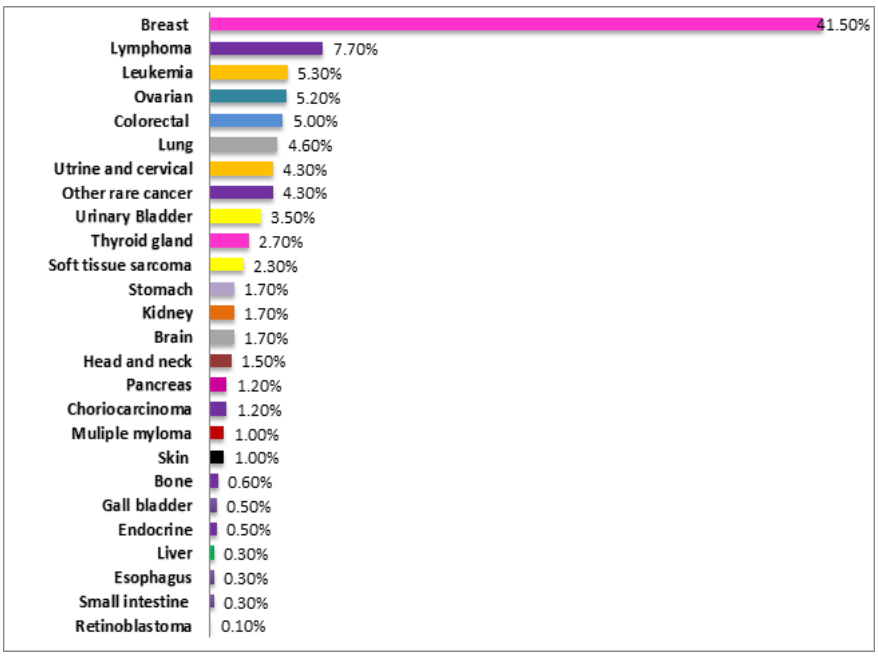


Figure 3. Incidence Rate of Cancer Types in Female

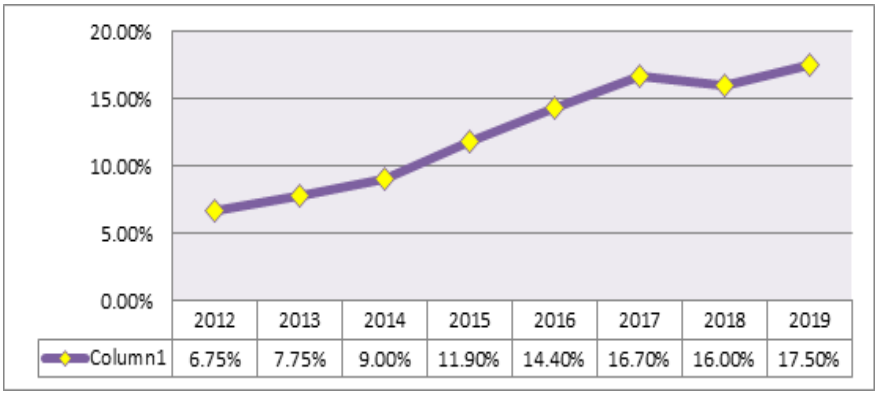


Figure 4. Percentage of Incidence Rate of Cancer Between 2012 to 2019

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424.
2. WHO, Iraqi Cancer Data for 2017-2018 announcement [cited February 2020]. Available from:http://www.emro.who.int/irq/iraq-news/cancer-data-for-20172018-announced-in-iraq.html .
3. Menkhi SA, Shanoon FH, Almayahi BA. Radiation pollution and cancer risks in Sulaimaniyah and Ninawa Cities, Iraq. Annu Res Rev Biol.2017 Oct 16:1-9.
4. Al-ShammariAM. Environmental pollutions associated to conflicts in Iraq and related health problems. Rev Environ Health. 2016 Jun 1;31(2):245-50.
5. Mjali A, Al-Shammari HH, Abbas NT, Azeez ZD, Abbas SK. Leukemia Epidemiology in Karbala province of Iraq. Asian Pac J Cancer Care. 2019;4(4):135-9.

DOI:10.31557/APJCC.2020.5.2.71

RESEARCH ARTICLE

Multiple Primary Tumours, How Frequent we Can Offer Curative Therapy?

Omima Elemam[1,2], Seham Abdelkhalek[1,3], Doaa Abdelmoety[4], Reem Baraka[5], Mervat Yousef[1,6]

[1]Oncology Center, King Abdullah Medical City, Makkah, Saudi Arabia. [2]Oncology Center, Mansoura University, Mansoura, Egypt. [3]Radiotherapy Department, Mansoura University, Mansoura, Egypt. [4]Research Center, King Abdullah Medical City, Makkah, Saudi Arabia. [5]Department of Biology, Colorado State University, Fort Collins, USA. [6]Radiotherapy Department, Assiut University, Assiut, Egypt.

Abstract

Background: Patients with Multiple-primary Malignancies are usually excluded from clinical trials. Clinical information re-distribution, associations, response to treatment and prognosis are scared. Collecting information will help us to expect the impact of prior therapies and to teach us how to best treat them. This study aims to report cases in our society and to see if we have a special predilection of certain Multiple-primary Malignancies in our region based on different geographic and environmental risk factors. Our retrospective study aims to collect these cases and follow their prognosis and treatment response as well as looking for any relation to cancer therapy. **Methods:** A retrospective study included patients who have two or more histologically diverse primary malignancy, either as synchronous or metachronous malignancy. The study was conducted in King Abdullah Medical City, Saudi Arabia over 7 years period from 2012 to 2019. We collected all patient's clinicopathological information, treatment, and modalities. **Results:** We collected 53 cases of multiple primary malignancies 26were synchronous (48%) and 27 were metachronous (52%). Out of 53 patients, 29 (60 %) were females and 14 (40 %) were males. The most common sites for synchronous are breast and endometrial cancer. Curative treatment could be offered in 19 patients (73%). For metachronous tumours, the most common primary tumour was breast cancer, while the most common second malignancy was colorectal cancer. Curative treatment could be offered in 15 patients (53%). **Conclusion:** Multiple primary malignancies represent a small proportion of our cases, with no special predilection in our society. Multiple primary malignancies did not signify a poor prognosis; besides non-metastatic cases showed a good response to therapy. We should not forget the possibility of a second primary tumour as these cases can be reasonably treated with curative intent.

Keywords: Double primary malignancy- Multiple primary malignancies- prognosis- cure rate- cancer risk

Asian Pac J Cancer Care, **5 (2)**, 71-78

Submission Date: 02/19/2020 Acceptance Date: 05/03/2020

Introduction

Multiple-primary cancers are defined as primary malignant tumours of different histological origins in a single patient. Recently, there has been an increase in the number of patients diagnosed with multiple-primary cancers; attributed to improved diagnostic techniques and prolonged life span of patients with malignancy. Now we are aware that most multiple primary cancers are double primary cancers [1-2-3].

The incidence of Multiple-Primary Malignancies has been common among cancer patients [4]. One of the earliest statistical analyses of Double-Primary Malignancies was carried out by Bugher in 1934, he derived an equation for the probability of death from cancer during a specified period of age with a coincidental Second Malignancy [5]. According to the definition used, the overall reported frequency of Multiple-Primary Cancers ranges from 2% to17% [6].

The criteria used for the diagnosis of Double-Primary

Corresponding Author:
Dr. Omima Elemam
Oncology Center, KAMC, KSA, Makkah, Saudi Arabia. Medical Oncology, Oncology Centre, Mansoura University, Mansoura, Egypt.
Email: omymaelemam@gmail.com

malignancies has been primarily given by Warren and Gates [7]. While, the two most commonly used definitions were provided by the SEER Program (Surveillance, Epidemiology, and End Results) and the IACR/IARC (International Association of Cancer Registries and International Agency for Research on Cancer) [8]. The SEER database considers single tumours at different sites in the same organ (e.g., colon) as multiple sites. The IACR/IARC rules are more limited; only one tumour is recorded for an organ, regardless of time, unless there are histologic differences. Additionally, The SEER database advocates the use of a 2-month period to distinguish between Synchronous and Metachronous Multiple-Primaries, whereas IARC recommends a 6-month period [9-10].

The theory regarding the origin of the majority of Multiple-Primary cancers is that they arise due to random chance, but different mechanisms have been suggested to be involved in Multiple-Primary Cancers, such as the family history, immunologic, genetic defects, exposure to carcinogens, radiation, chemotherapy, and field cancerization [11].

Germline mutations in mismatch repair genes can produce susceptibility to cancers of the colorectum, ovary, stomach, small bowel, upper uroepithelial tract, hepatobiliary tract, and brain. Li-Fraumeni syndrome (LFS), an autosomal- dominant disorder, features the occurrence of breast cancer in young women and of soft tissue sarcomas, osteosarcomas, brain tumours, acute leukaemia, and adrenocortical tumours in children and young adults [12]. Germline mutations in the p53 tumour suppressor gene (also known as TP53) have been identified in approximately one-half of LFS families in the literature [13] and cigarette smoking that affects the risk of several cancer types.

All the information about double malignancy came from case reports with very few centers reporting their experience and none from our region. We needed to collect our experience in treating those cases. Collecting information will aid us in expecting the impact of prior therapies and teach us how to best treat them.

This is a retrospective study with a single medical facility's experience with Multiple-Primary cancer cases. This study aims to report cases of Double-Primary Malignancy in our society and see if we have a special predilection of certain Double-Primary cancers based on different geographic and environmental risk factors.

Materials and Methods

This was a retrospective observational study carried out at King Abdullah Medical City, Makkah, Saudi Arabia, from January 2012 to December 2019. All Patients with malignant tumors of different histological origins were defines as histologically confirmed Multiple-Primary Malignancy cases. Patients were identified through a retrospective review of medical records excluding patients with insufficient histopathological data.

The data collected were the patients' characteristics, pathological data, and outcome information. Moreover, this research protocol was approved by the Institutional Review Board Committee. Since the study performed is retrospective, we obtained a waiver of informed consent from IRB.

Results

We collected 53 cases of Multiple-Primary malignancies 26 were synchronous (48%) and 27 were metachronous (52%). Out of 53 patients, 29 (60 %) were females and 14 (40 %) were males.

The most common sites for synchronous, Table 1, are breast and endometrial cancer. Metastasis at diagnosis was present in 7 patients (23%). The median age of diagnosis for synchronous tumours was 61 years (range: 27 to 83 years), 4 patients were male (26%). CT scan for staging workup resulted in the detection of a second tumour in 21 patients 5 patients of which was diagnosed during pathological examination. Curative treatment could be offered in 19 patients (73%).

For metachronous tumours, Table 2, the median age of diagnosis for the second primary neoplasm was 54years (range: 34 to 82years) 3 patients of which were male. The median interval of six years was observed, the most common sites of a primary tumour were breast, the most common second malignancy was colorectal cancer and Metastasis at diagnosis were present in 7 patients (25%). Curative treatment could be offered in 15 patients (53%).

Discussion

Multiple primaries [14] are more than one tumour arising in different sites and or of different histology either synchronous or metachronous depends on the duration between them, 2-month according to SEER data [15] and 6 months according to IARC. In our study, we used the definition of IARC. The burden of multiple tumours is expected to increase due to the use of accurate imaging techniques. In a single facility in Saudi Arabia, we collected 54 cases over 7 years. Multiple-Primary did not always signify a bad prognosis as we treated all non-metastatic cases with curative intent.

It is most imperative to diagnose it early before the patient reaches the metastatic stage. This means that we should have a high degree of suspicion. The role of the radiologist is crucial as usually, radiologists are first to flag for suspicion of multiple tumours. In our study, most of the synchronous tumours were detected initially by CT scan then confirmed pathologically. Examples from our study as CT scan done for a patient with ovarian cancer showed a breast mass or CT scan showed a speculated lung lesion in a patient with breast cancer or showed renal mass in a patient with nasopharyngeal cancer.

The response to therapy is always an alarm for the physician to review his pathology by repeating the biopsy of the metastatic disease. In our study a patient with breast cancer who developed lung nodules treated treated with chemotherapy as. Metastatic breast then the poor response to chemotherapy urged us to biopsy the largest metastatic nodule and to our surprise came to be second primary

Table 1. Patients with Synchronous Advanced Multiple Primary Tumours

Age At diagnosis	sex	Primary	Secondary	Detected by	Treatment	Metastasis at presentation	State of last follow up	Outcome /duration from diagnosis to death
79	F	Stage II breast cancer invasive ductal cancer (IDC)	Stage IV ovarian serous cancer	CT scan	Mastectomy and chemotherapy carboplatin/ Paclitaxel	yes	dead	Refused surgery for the ovary then received paclitaxel weekly then palliative care
68	F	Right breast IDC 11/2017	Stage IIIC high grade serous cancer	CT scan	TAH &BSO Omentectomy. Adjuvant Carbo/ paclitaxel No surgery for breast	No	Alive	Under follow up
61	F	Right breast IDC stage IIIB	Stage IIA colon cancer	CT scan	BCS ALND Chemotherapy FEC/ Docetaxel Sigmoidectomy letrozole	No	free	Under follow up
44	F	Right breast cancer IDC	Appendicular mucinous adenocarcinoma stage IV	CT scan	MRM tamoxifen	yes	dead	5 months
52	F	Left breast stage IIIA IDC	Stage IA endometrioid adenocarcinoma of the uterus	CT scan	TAH& BSO o mentectomy PLND Left MRM Chemotherapy FEC/docetaxel Radiotherapy Letrozole	No	free	Positive family history of ovarian cancer BRCA mutation positive Under follow-up
63	F	Breast IDC	Endometrial endometrioid adenocarcinoma	CT scan	Neoadjuvant with dual anti-HER 2 therapy. Followed by surgery for both	No	Alive	The patent currently under adjuvant therapy
63	F	Triple negative left breast IDC	Hormone receptor positive right breast cancer	Path exam	Neoadjuvant AC/ docetaxel Bilateral MRM	No	Alive	Currently under adjuvant hormonal therapy
65	F	Right breast IDC	Stage IV Rectal adenocarcinoma	CT scan	Right MRM Chemotherapy for rectal cancer	yes	Yes liver	Still under chemotherapy
75	F	Stage IVB endometrioid adenocarcinoma	Stage I mucinous carcinoma of the breast	CT scan	Carboplatin paclitaxel. But Refused surgery	yes	Dead	Refused surgery for the endometrium after very good response to chemotherapy
49	F	Stage IA endometrial endometrioid adenocarcinoma	Stage IA mucinous borderline tumour	Path exam	TAH &BSO infracolic omentectomy	No	free	Under follow up
36	F	Stage IA endometrial adenosequamus cancer	Papillary thyroid cancer	CT scan	TAH &BSO Total thyroidectomy	No	free	Underfollow up
64*	F	Stage IA endometrial endometrioid adenocarcinoma NSCLC stage T1bN0	Cancer rectum	CT scan	TAH &BSO Omentectomy+ Choleycystectomy Right lung lobectomy and hilar lymph node excision LAR	No	free	Under follow up
56	F	Stage I Uterine leiomyosarcoma	Stage IA Ovarian endometrioid borderline tumour	Path exam	TAH &BSO Omentectomy 7/2018	No	alive	Under follow up
72	F	Stage IA carcinosarcoma of the uterus	Stage I mucinous carcinoma of the breast	CT scan	TAH &BSO Followed by Adjuvant carboplatin/paclitaxel, Radiotherapy External pelvic Right MRM Adjuvant Letrozole	No	free	Relapsed 6 years later with metastatic carcinosarcoma shifted to palliative care after two cycles of chemotherapy

Continued Table 1.

Age At diagnosis	Sex	Primary	Secondary	Detected by	Treatment	Metastasis at presentation	State of last follow up	Outcome /duration from diagnosis to death
27	F	Left foot leiomyosarcoma	thymoma	CT scan	Surgery for both	No	free	Under follow up
39	F	Low grade brain glioma large infiltrative mass	Abdominal mass GIST	CT scan	Bilateral V/P shunt	No	dead	21 months
78	M	Stage IV nasopharyngeal cancer undifferentiated	Hepatocellular carcinoma Cirrhosis, LCF	CT scan	Radiotherapy incomplete course	yes	dead	6 months
47	F	Colon cancer high grade adenocarcinoma	Hodgkin's disease classical type stage IV	CT scan	ABVD	yes	dead	9 months
83	M	Rectal moderately differentiated cancer	Metastatic Prostate cancer GS4+4	CT scan	Goserelin / bicalutamide	yes	dead	8 months
69	M	Sigmoid adenocarcinoma T2N1	stageIIB Lung adenocarcinoma Lung carcinoid tumour low grade	CT scan	Surgery for both then adjuvant chemotherapy for lung carboplatin/ pemetrexed	no	Alive	Under follow up
60	F	Gastric adenocarcinoma T4N3M0	Lung mucinous adenocarcinoma	CT scan	Neoadjuvant chemotherapy ECF for gastric cancer, Gastrectomy then Lung lobectomy	N0	Dead	13 months
78	M	Prostate adenocarcinoma	Pleomorphic undifferentiated Sarcoma left femur	CT scan	Orchiectomy radiotherapy	no	Alive	Lost follow up
59	M	Renal cell carcinoma	Metastatic nasopharyngeal cancer	CT scan	Target therapy plus chemotherapy	yes	Alive	localized RCC refused surgery received pazopanib changed to sunitinib metastatic NPC received gemcitabine 10 cycles then start 2nd line docetaxel
68	F	Stage I gastric leiomyosarcoma	Stage I ovarian serous cancer	CT scan	Partial gastrectomy, ovarian cystectomy then Neoadjuvant carboplatin/paclitaxel then debulking surgery	no	free	Underfollow up
34	F	stage IA high grade ovarian mucinous cancer	Stage IA endometrioid adenocarcinoma	Path exam	TAH&BSO and omentectomy. Chemotherapy carboplatin/paclitaxel	no	free	Under follow up
45	F	Stage IC mucinous ovarian cancer	Stage IB endometrioid adenocarcinoma	Path exam	TAH&BSO and omentectomy. Chemotherapy carboplatin/paclitaxel Followed by radiotherapy	no	free	Under follow up

Lung Cancer.

Cancer patients who survive their primary tumour always have a high risk to develop a second primary and this is due to many reasons like genetic predisposition as one of our patients who has Double Synchronous Primary Breast Cancer and Endometrial Cancer gave a strong family history of ovarian cancer and her BRCA genetic testing came to be positive.

Cancer treatment is carcinogenic. We are reporting leukaemia in ovarian cancer patients treated with chemotherapy, breast cancer patients treated for DLBCL, and breast and thyroid cancer in Hodgkin's lymphoma patients treated at a young age.

For patients with breast cancer, the incidence of second primaries studied and has been reported to range from 4.1% to 16.4% [15-16]. An excess risk of endometrial cancer is reported with the use of Tamoxifen [17] Genetic factors as BRCA1 BRCA2 mutations are well-known risk factors for Multiple-Primary [18]. In this study, we reported 7 cases of the Synchronous Second-Primary with breast cancer, 3 cases with ovarian cancer. Also, we reported endometrial cancer in patients with hormone receptor-positive breast cancer with BRCA mutation. AML can be triggered during the first 2 years after radiation therapy and it is also a late effect of chemotherapy. For metachronous tumour in patients with breast cancer, We reported two cases of AML which may be chemotherapy related.

Patients with prostate cancer who received external beam radiotherapy are at increased risk of bladder cancer, rectal cancer and sarcomas within the radiation field after being disease-free for at least 5 years [19]. Second primaries can also occur in patients with prostate cancer owing to genetic factors, especially BRCA mutation [20]. In our study, we reported prostate cancer, rectal cancer, and prostate cancer and sarcoma synchronously.

The most important cause of mortality in Hodgkin's lymphoma is a Second-Primary cancer [21]. We reported a case of colon cancer synchronously with Hodgkin's lymphoma and thyroid cancer. Also, breast cancer that occurred 12 years after ABVD for Hodgkin's lymphoma.

Smoking is an important risk factor not only for lung cancer but also for a Second-Primary Cancer. A 7.9%of lung cancer cases who acquire a second primary have

Table 2. Patients with Metachronous Advanced Multiple Primary Tumours

Age	Sex	Primary	Treatment	Secondary	Treatment	Metastasis at presentation	Interval between primary and secondary	Recurrence
53	F	Stage I Breast IDC	Surgery hormonal letrozole	Stage II Colon cancer	Surgery, FOLFOX	No	7 y	
50	F	Stage III Breast IDC	Neoadjuvant chemotherapy EC/T Surgery, radiotherapy	Colon cancer T4N1M0	SUREGERY Capecitabine / Oxaliplatin	NO	14 Y	Colon cancer recurrence and received chemotherapy HIPEC and on chemotherapy
64	F	Stage II triple negative breast IDC	Surgery chemotherapy radiotherapy	Stage IV pancreatic cancer	Palliative care	yes	6 y	Died after 3 months
39	F	Breast IDC stage II	Surgery FAC Tamoxifen	Endometrium	Surgery radiotherapy	no	11 y	
44	F	Stage II breast IDC	Surgery TEC radiotherapy Tam /letrozole	Stage III Uterine carcinosarcoma	surgery carbo/paclitaxel		6 y	
42	F	STAGE IIA BREAST IDC	RT MRM TEC radiotherapy Tamoxifen	APL M5	ATRA	no	2 y	In CR Under follow up on Tamoxifen
35	F	Stage II breast IDC	Surgery FEC/ Docetaxel Radiotherapy tamoxifen	AML	FLAG then IDC.	no	5 y	In CR Under FU
51	F	Stage IIIA Breast cancer IDC Her2neu positive disease	Surgery chemotherapy Radiotherapy	Lung squamous cell lung cancer	Chemotherapy	no	2 y	Still under chemotherapy
47	F	ER+ breast cancer	Surgery and adjuvant chemo. Hormonal and radiotherapy	Stage IIA triple negative breast cancer	Surgery and chemotherapy	Yes	8 y	Under follow up
45	F	Papillary thyroid cancer	Surgery total thyroidectomy, radioactive iodine	Stage III Follicular lymphoma	FCR		3 y	Under follow up
41	F	Papillary Thyroid Cancer	Surgery radiotherapy	Stage IC Ovarian serous cancer	Debulking surgery Adjuvant chemotherapy	no	9 y	dead
72	M	Papillary Thyroid cancer	Thyroid surgery and ablation on replacement	Stage IV NSCLC	Chemotherapy and palliative radiotherapy	yes	20 y	dead
59	F	CML chronic phase	TKI Imatinib, desatinib	Colon cancer	Chemotherapy. Radiotherapy		9 y	Dead

Continued Table 2.

Age	Sex	Primary	Treatment	Secondary	Treatment	Metastasis at presentation	Interval between primary and secondary	Recurrence
35	F	CML	TKI	Tracheal adenocarcinoma	Surgery radiotherapy	no	15 y	In MMR Under follow up
70	F	Colon cancer	Surgery, XELOX	Breast	Docetaxel trastuzumab	yes	5 y	dead
68*	F	Stage II adenocarcinoma Colon cancer	Surgery radiotherapy chemotherapy	CML Then developed thyroid cancer	TKI Chemotherapy for colon	No	2 y	dead
80	F	HCC	HA chemoembolization	Breast cancer stage IV liver bone Mets	Trastuzumab Hormonal treatment	yes	2y	dead
70	F	Stage IV adenocarcinoma of the gall bladder	Surgery then gemcitabine	Stage colon cancer	Surgery chemotherapy FOLFOX / bevacizumab	yes	1y	dead
66	F	Stage endometrial endometrioid adenocarcinoma	Surgery	Breast DCIS	Surgery Tamoxifen	No	3 y	free
41	F	Stage II granulosa cell tumour of the ovary	Surgery chemotherapy VAC	Stage IV Carcinoid tumour of the pancreas	octreotide	yes	10 y	Under octreotide
82	F	Stage IA endometrial endometrioid Adenocarcinoma	Surgery	Stage I breast IDC	Hormonal and radiotherapy	no	1 y	free
65	F	Stage IIIc serous ovarian cancer	Neoadjuvant chemotherapy carboplatin / paclitaxel Interval debuing Adjuvant chemotherapy	Stage IV high grade neuroendocrine tumour	Refused chemotherapy	No	1y	dead
59	M	Cancer larynx T1N0M0	Radical Radiotherapy	Stage IV gastric cancer	Palliative chemotherapy and radiotherapy	Yes, liver Mets	2 y	dead
64	M	DLBCL stage IV B	Chemotherapy	Stage IIIB Mesothelioma	Chemotherapy	No	4 y	Under Chemotherapy
34*	F	Stage III B Hodgkin's lymphoma	ABVD	Papillary thyroid cancer And left breast cancer	Surgery radioactive iodine	No	12 y	Under follow up
55*	F	Stage IIA DLBCL	Chemotherapy and radiotherapy	Breast cancer stage and follicular lymphoma stage IA	Lumpectomy and ALND Chemotherapy Hormonal therapy for the breast Radiotherapy for FL	No	2y	Under follow up
54	F	Stage IIIA NHL follicular GII	Rituximab for 4 weeks and then maintenance	Hodgkin's lymphoma in axillary lymph node	AVD	No	2 y	Under follow up

*Triple malignancies; IDC, Invasive ductal carcinoma; DLBCL, diffuse large b cell lymphoma; TAH BSO, total abdominal hysterectomy and bilateral salpingoophrectomy; BCS ALND, breast conserving surgery and axillary lymph node dissection; MRM, modified radical mastectomy NSCLC non-small cell lung cancer; ABVD, Adriamycin, bleomycin vinblastine dacarbazine; AML, Acute myeloid leukaemia; APL, Acute promyelocytic leukaemia.

SCLC [22]. In this study, we reported colon cancer 1 year after lung cancer and gastroesophageal cancer that was diagnosed 18 months after the lung cancer diagnosis.

The treatment decision of synchronous tumours is not straightforward and usually requires a multidisciplinary approach, one of our patients had a synchronous breast and endometrial cancer. We discussed the case in our tumour board, and we decided to give her neoadjuvant chemotherapy followed by surgery MRM and TAH&BSO in the operating room by two surgeons.

We treated our patients with curative intent in more than 60% of cases so, we should always be aware of the possibility of a second primary cancer. Late metastatic spread in a patient with triple-negative breast cancer led us to suspect second primary and diagnose pancreatic cancer. Also, low tumour marker in ovarian cancer patient which was initially high was found to have a second primary neuroendocrine tumour, continued smoking history should alert us about this possible important carcinogen.

We should inform our patients about the late side effects of their treatment, particularly Second-Primary Malignancies, by including it in the consent form. Such actions would educate patients on the value of continuous surveillance and avoiding all possible carcinogens especially smoking in addition to encouraging them for a healthy lifestyle [23-24].

Patients with multiple primaries are usually excluded from clinical trials and there are no established guidelines to treat these cases. we need clinical trials to study the new histology non-specific medications like (immunotherapy, biologic therapy. etc)

Finally, in our medical facility, we adopted the policy of referring our cases with Multiple-Primary to our genetic oncology clinic for evaluation and genetic testing; this hopefully will help us gain more knowledge about patients with hereditary cancer. we will report these data separately.

In conclusion, we are expecting an increase in the prevalence of Multiple-Primary tumours due to increased accuracy of diagnostic techniques in addition to novel target therapy that may increase the risk. Hereditary cancer syndrome, smoking, cancer therapy are all risk factors. we need to pick these cases as early as possible before the development of metastasis as this has a marked impact on patient survival. Treatment decisions for these cases should be based on a multidisciplinary approach. Research on this topic is an unmet need particularly the genetic background for developing second primary cancers. To reflect more of a real-life population, we need clinical trials investigating those patients in detail to increase the physician's awareness that these cases are not rare, and they need to be treated with curative intent in most situations.

References

1. Siegel R, Miller K, Jemal A. Cancer statistics, 2019. CA: A Cancer Journal for Clinicians. 2019;69(1):7-34.
2. Noh S, Yoon J, Ryoo U, Choi C, Sung C, Kim T et al. A case report of quadruple cancer in a single patient including the breast, rectum, ovary, and endometrium. Journal of Gynecologic Oncology. 2008;19(4):265.
3. Lee J, Moon W, Park S, Park M, Kim K, Jang L et al. Triple Synchronous Primary Cancers of Rectum, Thyroid, and Uterine Cervix Detected during the Workup for Hematochezia. Internal Medicine. 2010;49(16):1745-1747.
4. Owen L. MULTIPLE MALIGNANT NEOPLASMS. JAMA: The Journal of the American Medical Association. 1921;76(20):1329
5. Bugher JC. The probability of the chance occurrence of multiple malignant neoplasms. Am J Cancer. 1934; 21(4):2309.
6. Vogt A, Schmid S, Heinimann K, Frick H, Herrmann C, Cerny T et al. Multiple primary tumours: challenges and approaches, a review. ESMO Open. 2017;2(2):e000172.
7. Warren S, Gates O. Multiple primary malignant tumours: A survey of the literature and statistical study. Am J Cancer. 1932; 16:1358–414.
8. Coyte A, Morrison D, McLoone P. Second primary cancer risk - the impact of applying different definitions of multiple primaries: results from a retrospective population-based cancer registry study. BMC Cancer. 2014;14(1).
9. Amer M. Multiple neoplasms, single primaries, and patient survival. Cancer Management and Research. 2014;:119.
10. Ferretti S. Airtum cancer registration handbook. Florence, Italy; 2009
11. Kim S, Kim H, Lee J, Lee Y, Kang W, Park J et al. Multiple Primary Cancers Including Colorectal Cancer. Journal of the Korean Society of Coloproctology. 2008;24(6):467.
12. Hartley A, Birch J, Kelsey A, Marsden H, Harris M, Teare M. Are germ cell tumors part of the Li-Fraumeni cancer family syndrome?. Cancer Genetics and Cytogenetics. 1989;42(2):221-226.
13. Frebourg T, Barbier N, Yan YX, Garber JE, Dreyfus M, Fraumeni J Jr., et al.Germline p53 mutations in 15 families with Li-Fraumeni syndrome. Am J Hum Genet 1995; 56:608-15.
14. Shah SA, Riaz U, Zahoor I, et al. Carcinoma multiplex. J Coll Physicians Surg Pak 2013; 23:290–2.
15. Amer M. Multiple neoplasms, single primaries, and patient survival. Cancer Management and Research. 2014;:119.
16. Weir H, Johnson C, Thompson T. The effect of multiple primary rules on population-based cancer survival. Cancer Causes & Control. 2013;24(6):1231-1242.
17. Ricceri F, Fasanelli F, Giraudo M, Sieri S, Tumino R, Mattiello A et al. Risk of second primary malignancies in women with breast cancer: Results from the European prospective investigation into cancer and nutrition (EPIC). International Journal of Cancer. 2015;137(4):940-948.
18. Molina-Montes E, Pérez-Nevot B, Pollán M, Sánchez-Cantalejo E, Espín J, Sánchez M. Cumulative risk of second primary contralateral breast cancer in BRCA1/BRCA2 mutation carriers with a first breast cancer: A systematic review and meta-analysis. The Breast. 2014;23(6):721-742.
19. Wallis C, Mahar A, Choo R, Herschorn S, Kodama R, Shah P et al. Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis. BMJ. 2016;:i851.
20. Friedenson B. BRCA1 and BRCA2 pathways and the risk of cancers other than breast or ovarian. MedGenMed 2005; 7:60.
21. Bhuller K, Zhang Y, Li D, Sehn L, Goddard K, McBride M et al. Late mortality, secondary malignancy and hospitalisation in teenage and young adult survivors of Hodgkin lymphoma: report of the Childhood/Adolescent/Young Adult Cancer Survivors Research Program and the BC Cancer Agency Centre for Lymphoid Cancer. British Journal of Haematology. 2016;172(5):757-768.
22. Bhaskarla A, Tang P, Mashtare T, Nwogu C, Demmy T,

Adjei A et al. Analysis of Second Primary Lung Cancers in the SEER Database. Journal of Surgical Research. 2010;162(1):1-6.
23. Hewitt M, Greenfield S, Stovall E, editors. From cancer patient to cancer survivor: lost in transition. Washington, DC: The National Academies Press; 2006.
24. Demark-Wahnefried W, Pinto B, Gritz E. Promoting Health and Physical Function Among Cancer Survivors: Potential for Prevention and Questions That Remain. Journal of Clinical Oncology. 2006;24(32):5125-5131.

DOI:10.31557/APJCC.2020.5.2.79

RESEARCH ARTICLE

Liver Resection in a Tertiary University Hospital in Damascus- trends Related to the Political Strife and Social Crisis

Basel Ahmad[1], Mohamad Essam Marwa[1], Khaled Turkmani[1], Tareq Ahmad[1], Ramez Baghdadi[1], Shaimaa Aboudamaah[1], Khetam Alkhatib[2], Mohamad Ahmad[3]

[1]Damascus University, Faculty of Medicine, Syrian Arab Republic. [2]Department of Internal Medicine, Al_Mouasat University Hospital, Damascus University Faculty of Medicine, Syrian Arab Republic. [3]Professor of Surgery, Head of Surgery Department, Faculty of Medicine, Damascus University, Chief of Liver Transplant Team, Al Assad University Hospital, Damascus.

Abstract

Background: Liver resection is a major operation requires technical training and experience and is expensive for the health care system. **Aim:** Our aim was to review trends in liver resection in Syria to help our country and others like Syria to understand the hardships for the country's health care policy. **Methods:** We analyzed retrospectively the results of 95 patients who underwent a liver resection from January 2009 through December 2015 at our tertiary university hospital in Damascus. **Results:** The number of annual liver resections increased over this 6 year period, but there were several years during which the numbers were dramatically less, related to the social crisis. Of them, 63 underwent resection for malignant neoplasms (66%) and 30 for non-malignant disorders (32%). **Conclusion:** Dedication of our surgeons to hepatic surgery is increasing in Syria with mortality rates close to international standards despite the ongoing social unrest and political strife.

Keywords: Liver resection- hepatectomy-social crisis- Damascus- Syria

Asian Pac J Cancer Care, **5 (2)**, 79-82

Submission Date: 02/20/2020 Acceptance Date: 05/04/2020

Introduction

Liver resection is the most efficacious treatment for patients with hepatic malignancies and selected benign diseases [1,2-3]. Improvements in various aspects of hepatic resections have led to better outcomes in recent decades. Our better comprehension of liver segmental anatomy improved assessment of appropriate candidates for such a major operation, and, immense progress in techniques of resection are important factors that have made liver resection a more common and safer operation [4]. The improved selection of patients and advances in perioperative management have decreased markedly the early postoperative mortality from 13% for all resections and > 20% for major resections to less than 8% [5].

Over the recent several decades, evidence has shown that operative resection of hepatic metastases can be undertaken safely in the majority of patients with resectable disease. This is especially true for patients suffering from colorectal liver metastases [6,7-8-9] patients with other neoplasms metastatic to the liver are potential candidates, but the outcomes are not as well documented.

Most prior studies of the results and frequency of liver resections have come mainly from European countries and East Asia with few studies from Middle-East countries.

The aim of our study was to evaluate our 7-year experience in a major tertiary referral hospital in Syria with liver resections, mainly the indications, perioperative features, and pathologic findings in order to detail risk factors and mortality of hepatectomy in the setting of political unrest and social crisis.

Materials and Methods

All patients who underwent liver resection At Al Assad University Hospital in Damascus, Syria between 1/1/2009

Corresponding Author:
Dr. Basel Ahmad
Damascus University, Faculty of Medicine, Syrian Arab Republic.
Email: dr.baselahmad@gmail.com

and 31/12/2015 were evaluated for inclusion in this study. Patients who had not resectable disease or had undergone radiofrequency ablation were excluded.

Standard demographic and clinic data were obtained, including age, sex, place of residency, blood group, pathology, history of smoking or alcohol use, history of diabetes or hypertension, days in Intensive Care Unit and postoperative hospitalization.

On presentation, all patients underwent a full history and physical examination, ultrasonography, and a multi-slice computed tomography; Magnetic resonance imaging was not available all the time. The decision to give neoadjuvant chemotherapy was made on a case by case basis according to the expected beneficial results. Resections were undertaken by the same operative technique and performed under maintenance of a low central venous pressure. Our operative team performed only open resections with the use of a Pringle maneuver and intraoperative ultrasonography used at the discretion of the surgeon. The hepatic parenchyma was divided by the clamp-crush technique or with the use of an energy-assisted device. The condition of the patient postoperatively was used to determine whether the patient needed ICU care or could be managed on the surgical floor.

Descriptive analyses were performed using IBM SPSS statistic version 23, and the missing data were excluded from analysis. This study was approved by the Research Ethics Committee, Faculty of Medicine, Damascus University (decision number 16-02-07).

Results

Between January 2009 and December 2015, 95 patients underwent a hepatic resection, including 43 male (45%) and 52 females (55%). The median age was 50 (range, 9–74) years; there were 4 patients less than 20 years old and one child less than 10 years old (Figure 1). Smoking habits were present in 22 patients (23%). 4 smokers (18%) had malignant neoplasms. Alcohol consumption was present in 6 patients (6%), 2 of whom had malignant neoplasms. Other co-morbidities included diabetes mellitus in 14 patients and hypertension was in 18.

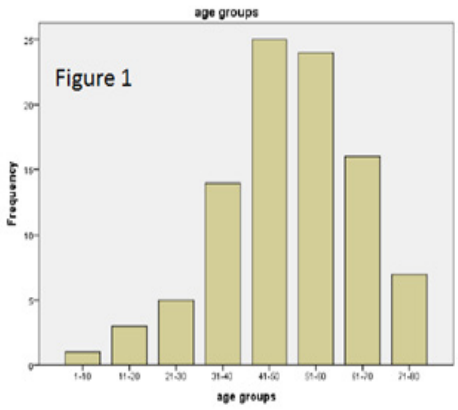


Figure 1. Age Distribution of the Patients Undergoing Hepatic Resection

Table 1. Type of Hepatic Resection

Type of Liver resection	N	Percentage
Nonanatomic segmental resections		
Single	19	20%
Two	12	12.6%
Three	1	1.1%
Four	1	1.1%
Anatomic		
S2-3	5	5.3%
S6-7	8	8.4%
Anatomic right hemiepatectomy	19	20%
Anatomic left hemiepatectomy	17	17.9%
Anatomic extended right hepatectomy	5	5.3%
Anatomic extended left hepatectomy	8	8.4%

In 2009, we performed only 10 hepatic resections. But in the years to follow, 2010 through 2015, we performed annually 17,6,12,16,13, and most recently in 2016, 21 hepatic resections, respectively. The median duration of stay in the hospital was 11 days, while the median duration of stay in the ICU for the 76 patients who required ICU care was 3 days.

Of 95 patients, 61 had anatomic resection (64%) and 34 had non-anatomic resection (36%). Table 1 shows the types of resection. There were 63 patients who underwent hepatic resection for malignant neoplasms (66%) and 30 for non-malignant tumors (32%). Seven patients died during operation or within days of hospitalization. The mean number of units of blood, plasma, and platelets used during the operation and hospitalization was 3.3, 3.2, 0.6 units, respectively; 13 patients never requited any blood products.

Discussion

Hepatic resection is now firmly established as the most effective treatment for patients with primary hepatobiliary malignancies, selected patients with certain extrahepatic malignant neoplasms metastatic to the liver, and some benign disorders involving the liver [10-11].

Smoking is considered one of the most important risk factors for the development of early complications after partial hepatectomy. We have closely smokers' ratio to others studies. Alcohol is one of the Common causes of existing liver disease but we have low value compared to other studies, this could be due to our traditions [12-13].

The annual number of formal liver resections has increased since 2009. But as seen, this increase was disrupted from 2011 through 2014 during the especially difficult times for our country. Our ongoing civil war has disrupted the ready ability to refer patients to our university hospital. Despite these hardships, we have worked hard to provide the services needed to those who could find the way to present at our university hospital. Much of what we have been able to accomplish is related

to the unwavering dedication of our medical personnel whose goal is to provide the best care possible to our citizens.

Patients with greater levels of postoperative pain tend to have more complications after surgery, longer hospitalization leading to higher medical costs, and lower levels of patient satisfaction [14]. The duration of hospitalization may not reflect surgeon/institution performance, because in these times of strife, the appropriate time for discharge is multifactorial and likely related to the population, patient selection, and increased high-risk cases with a surgeon's experience [15]. In this study, we achieved close and reasonable ratio to the rest of the studies [16,17-18].

In our study, we also have identified the geographic distribution of residential areas subject to the liver and found that Damascus and its countryside is the most frequent place of residency of patients, not to forget that the main liver surgery center in Syria is in the hospital of our study in Damascus.

Consumption of banked blood may reflect the degree of blood loss [19-20]. However, the mainstay to prevent bleeding is crucial during hepatectomy [21-20]. Our mean blood unit and plasma unit is less than some other studies [22].

The functional residual hepatic reserve must be considered for any liver resection [23]. This has been of course one of our considerations in doing any formal hepatic resections and post-surgery hepatic failure and deterioration in liver function were studied in our previous paper [3]. In addition, surgical stress can be decreased by non-anatomic resections when appropriate, which may affect perioperative morbidity and mortality [24-25]. Several studies reported shorter operating times and significantly less blood loss after non anatomic resections [26-27]. Thus we have tried to use these non-anatomic resections when appropriate, especially for metastatic lesions and for non-malignant conditions.

Laparoscopic resection is now carried on some countries showing similar results to open technique but unfortunately it is still not carried on in Syria due to lack of appropriate laparoscopic equipment and experience. However, Dedication of our surgeons to hepatic surgery may lead to perform this in the near future just like (the liver transplantation team in AlAssad university hospital in Damascus) performed the first liver transplantation in Syria in the beginning of 2016.

In our series, there were seven deaths during operation or hospitalization: four in the Anatomic resection group, and three in the non-anatomic resection group, which was not significantly different. There are studies suggesting more postoperative deaths After an anatomic resection [27-28].

In conclusion, liver resection surgery is still being performd and appears to be increasing in Syria despite the political and social unrest in our country. With the dedication and hard work of our health care providers, we have been able to provide the expertise needed to accomplish relativelysafe and successful liver resections with morbiditiy and mortality rates close to the rates described elsewhere in the world.

Conflict of interest

There is nothing to disclose.

References

1. Imamura H, Seyama Y, Kokudo N, Maema A, Sugawara Y, Sano K, et al. One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg 2003;138(11):1198–206; discussion 1206.
2. Charny CK, Jarnagin WR, Schwartz LH, Frommeyer HS, DeMatteo RP, Fong Y, et al. Management of 155 patients with benign liver tumours. Br J Surg 2001;88(6):808–13.
3. Ahmad B, Turkmani K, Marwa ME, Ahmad T, Baghdadi R, Aboudamaah S, et al. Perioperative Liver Function after Hepatectomy in a Tertiary University Hospital in Damascus. Asian Pac J Cancer Prev 2017;18(8):2109–2113.
4. Sugarbaker PH. Surgical decision making for large bowel cancer metastatic to the liver. Radiology 1990;174(3):621–626.
5. Belghiti J, Regimbeau JM, Durand F, Kianmanesh AR, Dondero F, Terris B, et al. Resection of hepatocellular carcinoma: a European experience on 328 cases. Hepatogastroenterology;49(43):41–6.
6. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: A systematic review of published studies. Br J Cancer 2006;94(7):982–999.
7. Wei AC, Greig PD, Grant D, Taylor B, Langer B, Gallinger S. Survival After Hepatic Resection for Colorectal Metastases: A 10-Year Experience. Ann Surg Oncol 2006;13(5):668–676.
8. Leporrier J, Maurel J, Chiche L, Bara S, Segol P, Launoy G. A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. Br J Surg 2006;93(4):465–474.
9. Sjövall A, Järv V, Blomqvist L, Singnomklao T, Cedermark B, Glimelius B, et al. The potential for improved outcome in patients with hepatic metastases from colon cancer: a population-based study. Eur J Surg Oncol 2004;30(8):834–41.
10. Agrawal S, Belghiti J. Oncologic Resection for Malignant Tumors of the Liver. Ann Surg 2011;253(4):656–665.
11. Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: An update. Hepatology 2011;53(3):1020–1022.
12. Lv Y, Liu C, Wei T, Zhang J-F, Liu X-M, Zhang X-F. Cigarette smoking increases risk of early morbidity after hepatic resection in patients with hepatocellular carcinoma. Eur J Surg Oncol 2015;41(4):513–9.
13. Park SK, Jung YK, Chung DH, Kim KK, Park YH, Lee JN, et al. Factors influencing hepatocellular carcinoma prognosis after hepatectomy: a single-center experience. Korean J Intern Med 2013;28(4):428.
14. Joshi GP, Ogunnaike BO. Consequences of Inadequate Postoperative Pain Relief and Chronic Persistent Postoperative Pain. Anesthesiol Clin North America 2005;23(1):21–36.
15. Lorenzo CSF, LIMM WML, Lurie F, Wong LL. Factors affecting outcome in liver resection. HPB 2005;7(3):226–230.
16. Wang H-Q, Yang J, Yan L-N, Zhang X-W, Yang J-Y. Liver resection in hepatitis B related-hepatocellular carcinoma: clinical outcomes and safety in elderly patients. World J Gastroenterol 2014;20(21):6620–5.

17. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg 2002;236(4):397-406; discussion 406–7.
18. Moss CR, Caldwell JC, Afilaka B, Iskandarani K, Chinchilli VM, McQuillan P, et al. Hepatic resection is associated with reduced postoperative opioid requirement. J Anaesthesiol Clin Pharmacol 2016;32(3):307–13.
19. Yuasa T, Niwa N, Kimura S, Tsuji H, Yurugi K, Egawa H, et al. Intraoperative blood loss during living donor liver transplantation: an analysis of 635 recipients at a single center. Transfusion 2005;45(6):879–84.
20. Devi A. Transfusion practice in orthotopic liver transplantation. Indian J Crit Care Med 2009;13(3):120.
21. Mor E, Jennings L, Gonwa TA, Holman MJ, Gibbs J, Solomon H, et al. The impact of operative bleeding on outcome in transplantation of the liver. Surg Gynecol Obstet 1993;176(3):219–27.
22. Kaibori M, Saito T, Matsui K, Yamaoka M, Kamiyama Y. Impact of fresh frozen plasma on hepatectomy for hepatocellular carcinoma. Anticancer Res;28(3B):1749–55.
23. Adam R, Wicherts DA, de Haas RJ, Ciacio O, Lévi F, Paule B, et al. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? J Clin Oncol 2009;27(11):1829–35.
24. Gold JS, Are C, Kornprat P, Jarnagin WR, Gönen M, Fong Y, et al. Increased use of parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. Ann Surg 2008;247(1):109–17.
25. Kokudo N, Tada K, Seki M, Ohta H, Azekura K, Ueno M, et al. Anatomical major resection versus nonanatomical limited resection for liver metastases from colorectal carcinoma. Am J Surg 2001;181(2):153–9.
26. Finch RJB, Malik HZ, Hamady ZZR, Al-Mukhtar A, Adair R, Prasad KR, et al. Effect of type of resection on outcome of hepatic resection for colorectal metastases. Br J Surg 2007;94(10):1242–8.
27. Stewart GD, O'Súilleabháin CB, Madhavan KK, Wigmore SJ, Parks RW, Garden OJ. The extent of resection influences outcome following hepatectomy for colorectal liver metastases. Eur J Surg Oncol 2004;30(4):370–6.
28. Zorzi D, Mullen JT, Abdalla EK, Pawlik TM, Andres A, Muratore A, et al. Comparison between hepatic wedge resection and anatomic resection for colorectal liver metastases. J Gastrointest Surg 2006;10(1):86–94.

DOI:10.31557/APJCC.2020.5.2.83

RESEARCH ARTICLE

A successful Model of Cancer Screening in Low Resource Settings: Findings of an Integrated Cancer Screening Camp from a Rural Setting of North India

Bashar MD Abu[1], Aggarwal Arun K[2]

[1]Department of Community Medicine, MM Institute of Medical Sciences & Research, MM Deemed University, Mullana, Haryana, India. [2]Department of Community Medicine & SPH, PGIMER, Chandigarh, India.

Abstract

Background: Cancers of cervix, breast and oral cavity claims millions of deaths each year globally and are the three most common cancers in India. There is need to develop and test models for organizing integrated cancer screening camps in low resource settings with inter-sectorial co-ordination between different stakeholders. **Methods:** A community based integrated cancer screening camp was organized in a rural setting of north India in co-ordination with district health administration and local governing body (Panchayati Raj Institution). Screening methods included Clinical Breast Examination (CBE) for breast cancer, visual inspection under 5% acetic acid (VIA) for cervical cancer and oral visual examination (OVE) for oral cavity cancer. Men and women found to be screen positive in the camp were referred to the district hospital and a tertiary care center for further diagnostic tests and were followed up. **Results:** A total of 90 individuals (40 men and 50 women) above 30 years of age attended the screening camp. Of them, one (2.5%) male was screened positive for precancerous lesion of oral cavity. Out of the 50 women attending the camp, two were detected with suspected breast lumps, which on further diagnostic tests at district hospital were diagnosed as benign tumors. Only half (52.0%) of the women consented for cervical cancer screening, out of which one (3.9%) was screened positive on VIA which on colposcopy examination and biopsy at referral center was confirmed as early stage cancerous lesion of cervix and was instituted on treatment. **Conclusion:** The screening camp sets a successful example of community based cancer control activity for early detection and management of three common cancers through inter-sectoral co-ordination in low resource settings.

Keywords: Cancer screening- clinical breast examination- VIA- oral visual examination- low resource settings

Asian Pac J Cancer Care, **5 (2)**, 83-86

Submission Date: 02/24/2020 Acceptance Date: 05/04/2020

Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases annually [1]. It is the second leading cause of mortality globally and was responsible for 8.8 million deaths in the year 2015 with 70% of these deaths occurring in low and middle income countries (LMICs) only [2].

Early detection of cancer greatly increases the chances for successful treatment. There are two major components of early detection of cancer: health promotion including education and early diagnosis through screening [3]. World Health Organization recommends early detection through screening of at risk population for common cancers of the breast, cervix, mouth, larynx, colon and rectum, and skin [3]. However, screening programs should be undertaken when prevalence of the disease is high enough to justify the effort and costs of screening and when facilities exist for follow-up of those with abnormal results to confirm diagnoses and ensure treatment [4].

Breast and cervical cancers are the most common cancers in Indian women [5]. However, they are easily amenable to screening methods. For breast cancer, it is

Corresponding Author:
Dr. Bashar, MD Abu
Department of Community Medicine, MM Institute of Medical Sciences & Research, MM Deemed University, Mullana, Haryana, India.
Email: imback20006@yahoo.in

recommended to have Breast Self-Examination (BSE) aided by clinical breast examination [6]. For cancer cervix, visual inspection of cervix under acetic acid (VIA) and Visual Inspection with Lugol's Iodine (VILI) are recommended for any low resource-settings [7]. Similarly, oral cancers can easily be screened by visual inspection of oral cavity even by primary health care workers and trained non-medical personnel [8].

As these three common cancers can be screened in any low resource settings, we organized a cancer screening camp in a rural setting for screening and early detection of these three cancers.

Materials and Methods

An integrated cancer screening camp was organized in village Kheri of Raipur Rani Community Development Block in district Panchkula of Haryana, North India which is the rural field practice area of the department of Community Medicine, PGIMER, Chandigarh. Government Middle School within the village was chosen as the site for the camp. District health administration and local governing body participated actively. The village, where the camp was organized, had a total population of 1680. The village Sarpanch (local elected village leader under Panchayati Raj Institution), other PRI members and the community health workers like ANMs and ASHAs disseminated information about the camp in the adjoining villages, starting one month prior to the camp. The eligible population for screening was chosen as those 30 years or above of either sexes willing to undergo screening and were not diagnosed previously with these cancers. Informed oral consent was taken before screening of the eligible participants.

Health Work Force for Camp

District civil surgeon deputed one Gynecologist and one specialist Dental Surgeon from the nearby Community Health Centre (CHC) and District Hospital. Principal Medical Officer deputed two staff nurses trained in conducting cervical cancer screening. From the department of Community Medicine, PGIMER, one faculty member, one senior resident and two junior residents participated. In addition, school teachers and local village volunteers were actively involved for motivating the villagers to undergo screening.

Set up of the cancer screening site

Screening for the three cancers was performed in three separate different rooms to maintain confidentiality and privacy. Appropriate labels in local language were displayed at the entrance of each room. Participants were explained about the benefit of the screening tests through health talks and only those who consented were screened.

Three teams were formed: 1) For breast cancer education and screening 2) For cervical cancer screening and 3) for oral cancer screening. These teams were given separate rooms in the sequence as depicted in Figure 1.

In common area for Health Education, health talk was imparted to the participants about the three common cancers, their risk factors and importance of early detection and management. They were also told about the importance of periodic checkups even if they do not have any signs or symptoms. At the end, participants were instructed to move to appropriate rooms for the screening after taking consent.

In room number 1, the dental surgeon assisted by dental assistant did screening for oral cancer by Oral Visual Examination (OVE) of all the participants. In room 2, the gynecologist assisted by two staff nurses and one female health worker, did screening for cervical cancer by visual inspection of cervix with 5% acetic acid (VIA) technique as per the International Agency for Research on Cancer manual and chart [9]. System was setup such that sterilized speculums always remained available irrespective of the number of women who may report for examination. Time taken to examine each woman and time to disinfect a speculum was taken into consideration to plan the number of speculums required for camp.

In room 3, a team of two female resident doctors showed 10-minute video on Breast Self-Examination, to the participants in batches of about 10. It was then followed by Clinical Breast Examination (CBE) in sitting and lying down position by the resident doctors as per the modified version of the Canadian National Breast Screening Study protocol [10].

Results

A total of 90 individuals (40 men and 50 women) above 30 years of age attended the screening camp. Majority of the participants were in the age group 40-49 years (Table 1). All the 50 women consented to undergo screening for breast cancer out of which two were found to have suspected breast lump on CBE (Table 2) and were referred to district hospital for confirmatory investigations. Both cases complied with the referrals and based on further investigations, such as Mammography, USG and FNAC, were diagnosed as cases of fibro adenoma, a benign lesion of breast. Out of the 50 women, only 26 consented to undergo screening for cervical cancer through VIA technique out of which one was screened positive (Table 2) and was finally diagnosed with cervical squamous intraepithelial neoplasia-2 (CIN-2), an early stage cancerous lesion of cervix based on colposcopy

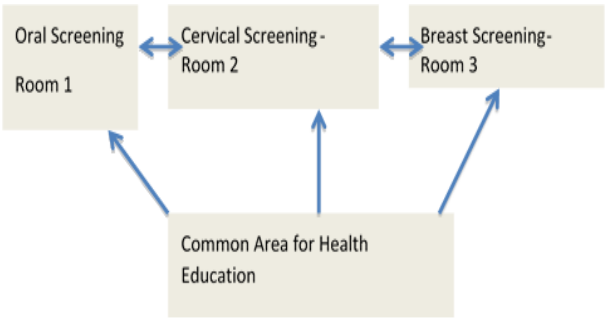


Figure 1. Set up of the Integrated Cancer Screening Camp at Kheri village of Haryana, North India

Table 1. Socio-demographic Characteristics of the Camp Participants (N=90)

Variables	Number (%)
Sex	
Male	40 (44.4)
Females	50 (55.6)
Age group (in years)	
30-39	20 (22.2)
40-49	40 (44.4)
50-59	21 (23.3)
60 and above	09 (10.0)
Education	
Illiterate	34 (37.8)
Up to primary level (5th class)	28 (31.1)
Up to Middle (8th class)	16 (17.8)
Up to Matriculation & Above	12 (13.3)
Occupation	
Housewife	36 (40.0)
Unskilled Labour	22 (24.4)
Farming	16 (17.7)
Govt. employee	08 (8.9)
Unemployed/retired	08 (8.9)
Total monthly income (in Indian National Rupees)	
>5000	04 (4.4)
5000-10,000	30 (33.3)
10,001-15,000	32 (35.6)
15,001-20,000	16 (17.8)
Above 20,00	08 (8.9)

examination and biopsy test at PGIMER, Chandigarh and was instituted on treatment from there.

All the 90 participants consented to undergo screening for oral cavity cancer, out of which one male participant was found to have leukoplakia, a pre-malignant lesion of oral cavity (Table 2). The person was a chronic bidi smoker and habit of chewing tobacco. He was informed about the risk of the lesion to turn malignant and counseled for quitting smoking and tobacco chewing.

Discussion

Increasing community awareness about cancer and screening for common cancers provides the most cost effective approach for prevention and control of cancers and has high public health potential [11]. To move towards Universal Health Care Coverage (UHC) [12], health systems should devise mechanisms to include NCDs including cancer screening and management in the health care package at district and sub-district level.

There are many strengths of our experience. First, using World Cancer Day, all-important sectors were sensitized and involved. All sectors like district and sub-district level health system, PRIs, local education department and department of Community Medicine of a tertiary care institute, as nodal coordinating department, contributed. Thus for achieving UHC, if one needs to add a new service, this model demonstrates – how to use some important public health day like World cancer day, involve the political and health system leaders and demonstrate them the service provision in a limited population. Same service can then be extended to other populations with their support without financial burden on the population- achieving all three dimensions of UHC [11]. This model also demonstrates that inter-sectoral coordination can not only help mobilize the resources but it also increases the stake of possible stakeholders.

Secondly, acceptability of the population for breast cancer and oral cancer screening was high as everyone consented to undergo these giving an acceptance rate of 100%. However, for cervical cancer screening only 52.0% of the women consented. There are other experiences from India where cervical cancer screening rates were reported to be somewhat higher [13-14] This may be due to different methodology followed in organizing these screening camps. In the study by Mishra et al, Tata memorial hospital, Mumbai had setup a community based cancer screening program with strong component of Heath Education Program (HEP). Program had strong house to house survey, followed by HEP, before actual screening was done [12]. In this model, they had used 10th grade qualified workers after providing 3 months training, to screen the population for cancers. Project staff did the screening activity and other sectors were not actively involved. In the study by Sharma et al from Delhi, cervical cancer screening camp was set up at Primary Health Centre level. In these camps, Pap smear as screening test was done among women who clinically were found to have some reproductive morbidity [13]. There are some other examples of organizing camps for breast cancer screening [15-16]. Most of these screening camps were organized at health facilities at district or sub-district level. In this context our experience of organizing an integrated cancer screening camp at village level in community setting at village level by involving specialists and creating professional setup for examination with inter-sectoral coordination can be considered successful and a unique model.

It may be argued that diagnostic yield in our camp was less. Only one woman (3.99%) out of 26 screened for

Table 2. Screening Results of the Integrated Cancer Screening Camp in Rural Haryana (N=90)

Cancer Screened	Number of individuals Screened	Number (%) screened Positive
Oral	90	1 (1.1)
Breast	50	2 (4.0)
Cervical	26	1 (3.9)

cervical cancer was found positive on VIA and 2 (4.0%) out of 50 screened for breast cancer had suspicious breast lumps. Reports of other camps available in published literature show that at most places only symptomatic or pre-screened eligible populations were screened further for cancer screening. In a screening camp at Raichur, Karnataka, 7 out of the 22 women having complaints of reproductive tract morbidities undergoing screening, had suspicious malignancy on Pap smear [17]. The study by Sharma et al also reported prevalence of 7.1% carcinoma in situ or high grade carcinoma on Pap smear among women who were clinically having any reproductive morbidity [14]. In the Mumbai study done on large population with extensive health education and targeted screening of women having some pre-eligibility criteria, cancer cervix screen positives were 14.9% [13]. Less diagnostic yield in our camp may be due to the fact that no such prescreening was done and women in all reproductive age groups were invited for examination irrespective of their symptom status. On the spot 20 minutes' health education talk was imparted to highlight the need and significance of periodic examinations and the fact that any woman may have cancer without experiencing any symptoms. With this minimal effort, about 50% of the women got themselves screened for cervical cancer. In Mumbai study, even with extensive efforts, only 70% women came forward for screening [12]. We believe that with additional health educational efforts during the weeks preceding the camp, screening output could have been increased.

In conclusion, our model of community based integrated cancer screening camp for three common cancers sets a successful example of cancer control activity in low resource settings. Two cases of undiagnosed pre-cancerous lesions were detected in the camp which shows its success for early detection of cancers. The current model of organizing integrated cancer screening camp for common cancers may be scaled up for cancer screening and prevention for common cancers in all low resource settings at district, state and country level in low and middle income countries.

Conflict of interest None declared

Source of funding Funding to organize the camp was provided by district health administration and local governing body i.e. Panchayati Raj Institutions (PRIs)

References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11. Lyon, France: International Agency for Research on Cancer; 2013.
2. World Health Organization. Cancer Fact sheet. Available from: http://www.who.int/mediacentre/factsheets/fs297/en/ [last accessed on 16 December, 2018]
3. World Health Organization. Early detection of cancer. Available from: http://who.int/cancer/detection/en/ .[last accessed on 16 December, 2018]
4. World Health Organization. Cancer. Screening. Available from: https://www.who.int/cancer/prevention/diagnosis-screening/screening/en/ [Last accessed on 16 December, 2018]
5. Asthana S, Chauhan S, Labani S. Breast and cervical cancer risk in India: An update. Indian J Public Health 2014; 58:5-10.
6. World Health Organization. Breast cancer: prevention & control. Available from: http://who.int/cancer/detection/breastcancer/en/ [last accessed on 16 December, 2018].
7. World Health Organization. Screening for cervical cancer. Available from: http://who.int/cancer/detection/cervical_cancer_screening/en/ [last accessed on 16 December, 2018]
8. World Health Organization (2017e). Screening for oral cancer. Available from: http://who.int/cancer/detection/oralcancer/en/ [last accessed on 16 December, 2018].
9. Sankaranarayanan R, Wesley R (2003). A Practical Manual on Visual Screening for Cervical Neoplasia. IARC Technical Publication No. 41. Lyon, IARC Press.
10. Basset AA (1985): Physical examination of the breast and breast self-examination; in Miller AB (ed.): Screening of Cancer. Orlando, Academic Press.
11. World Health Organization (2002). National cancer control programmes: policies and managerial guidelines. Geneva, Switzerland: WHO.
12. World Health Organization. Health financing for universal coverage. Available from http://www.who.int/health_financing/universal_coverage_definition/en/ [Last accessed on 16 December, 2018]
13. Mishra GA, Dhivar HD, Gupta SD, Kulkarni SV, Shastri SS. A population-based screening program for early detection of common cancers among women in India –methodology and interim results. Indian J Cancer 2015; 52:139-45.
14. Sharma P, Rahi M, Lal P. A Community-based Cervical Cancer Screening Program among Women of Delhi using Camp Approach. Indian J Community Med. 2010 Jan; 35(1): 86–88.
15. Reddy N, Ninan T, Tabar L, Bevers T (2012). The Result of Breast Cancer Screening Camp at a District Level in Rural India. Asian Pacific J Cancer Prev, 13, 6067-6072.
16. Jose R. Breast Cancer Awareness and Screening: A New Approach. Academic Medical Journal of India. 2015. Dec 28; 3(4):1-2.
17. Ade A. Cervical cancer screening. Int J Reprod Contracept Obstet Gynecol 2014; 3:868-9.

DOI:10.31557/APJCC.2020.5.2.87

RESEARCH ARTICLE

Epidemiology, Pattern of Recurrence and Survival in Triple-negative Breast Cancer: A Retrospective Analysis

Dharmendra Singh, Niladri Roy, Sumana Maiti Das

Department of Radiotherapy, Institute of Post Graduate Medical Education and Research, Kolkata, India.

Abstract

Background: Breast cancer is the most common cancer in the world. Triple-negative breast cancer (TNBC) characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and Her2neu receptor. This study investigated the epidemiological characteristics and survival in non-metastatic TNBC. **Materials and methods:** Data from medical records of patients with breast cancer between 20014 and 2018 were retrieved, and patients with TNBC were identified and analyzed for demographic and clinicopathological features. Survival analyses were performed using the Kaplan–Meier method for disease-free survival (DFS) and overall survival (OS). **Results:** A total of 457 nonmetastatic breast cancer patients were registered at our institute from January 2014 to August 2018, of which 137 were triple-negative breast cancer (TNBC). This accounted for 29.9% of nonmetastatic breast cancer during this period. With the median age of 45 years at diagnosis, the most common presenting complaint was breast lump. The median duration of symptoms was 30 months. The most commonly affected age group was 41-50 years. The majority of the patients were in a locally advanced stage (69.3%) while 30.7% were in the early stage. 29.2% recurrence at 38 months of median follow up. Recurrence was statistically significantly correlating with age ≤ 35 ($p = < 0.001$), pathological stage ($p = < 0.001$), nodal status at diagnosis ($p = < 0.001$), perineural invasion (PNI) ($p = < 0.001$), number of positive lymph nodes ($p = < 0.001$). The mean DFS and OS were 43.6 and 46 months respectively. 3-year DFS and OS were 65.5% and 66.2 % respectively. **Conclusion:** TNBCs are high-grade tumors mostly presented in locally advanced stages and most of the patients are young. TNBCs are clinically aggressive with high risk of metastasis to visceral organs. The survival of TNBCs in the Indian scenario is poor in comparison to Western populations, probably due to racial factors, socioeconomic factors and health care access facility.

Keywords: Triple-negative breast cancer- poor prognosis of TNBC- lymph node ratio- survival

Asian Pac J Cancer Care, **5 (2)**, 87-94

Submission Date: 02/25/2020 Acceptance Date: 05/04/2020

Introduction

Breast cancer is the most common cancer diagnosed annually, as per GLOBOCAN 2018 data the incidence and mortality of breast cancer is 11.6% and 6.6% respectively [1]. Breast cancer is the leading cause of cancer-related death among women around the world. Breast cancer is the most frequently observed cancer (14% of the total cases) and it is the leading cause of cancer death (11·1% of the total cases) in India [2]. In India among the females breast cancer is the most common cancer with an incidence of 27.7%. In developing countries, about half the breast cancer cases and 60% of the deaths estimated to occur [3]. Breast cancer is one of the most complex diseases in terms of cellular origin, tumor pathology, molecular subtypes, gene mutations, metastatic pattern, disease progression, therapeutic response and clinical outcome [4-5]. Breast cancer can be subclassified into different subtypes on the basis immunohistochemical (IHC) protein overexpression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor type 2 (Her2neu) as luminal A (ER-positive; Her2neu-negative), luminal B (ER-positive; Her2neu-positive); Her2neu enriched

Corresponding Author:
Dr. Dharmendra Singh
Department of Radiotherapy, Institute of Post Graduate Medical Education and Research, Kolkata, India.
Email: babu.dsingh.singh35@gmail.com

(ER-negative; Her2neu-positive) and triple-negative or basal-like (ER-negative; Her2neu-negative) [6-7]. The triple-negative breast cancers (TNBC) are considered as most malignant subtypes as these subtypes are associated with increased tumor size, increased incidence of axillary lymph node involvement and poor prognosis as compared to other subtypes [8, 9-10]. TNBC accounts for approximately 12% to 17% of all invasive breast cancers in Western populations. This study was aimed to investigate the epidemiological characteristics and survival in non-metastatic TNBC presented at a tertiary care center at Kolkata.

Materials and Methods

Data from the medical records of patients attending the department of Radiotherapy at the Institute of Post Graduate Medical Education and Research (IPGME&R), Kolkata were retrieved between January 2014 to August 2018 of non-metastatic TNBC were identified and analyzed after approval from Institutional Ethics Committee. Tumors with IHC of ER, PR with expression ≤1% and a score of 0 or +1 for Her2neu considered as TNBC. IHC for Her2neu having a score of +2 were considered for fluorescence in situ hybridization (FISH) and those with FISH negative for Her2neu also considered as Her2neu negative. IHC done on formalin-fixed paraffin-embedded sections by polymer horseradish peroxidase technique. Patients with TNBCs classified histopathologically according to WHO classification [11]. Histological grade of tumors was determined using Nottingham histological score [12]. All the patients were staged according to the American Joint Committee on Cancer (AJCC TNM) 7th edition. Patients with stage I, IIA and a subset of IIB (T2N1M0) considered as early breast cancer (EBC) while a subset of stage IIB (T3N0M0), IIIA, IIIB and IIIC as locally advanced breast cancer (LABC). The morphological parameters analyzed were tumor size, histological type, histological grade, Lymphovascular invasion (LVI), perineural invasion (PNI), number of involved lymph nodes, total number of lymph nodes in the specimen and lymph node ratio (ratio of involved lymph nodes to the total number of lymph nodes in the post-operative specimen). The information was entered into pre-designed Performa followed by analysis of epidemiological characteristics, survival and their correlations. Disease-free survival (DFS) was defined from the start of primary therapy to the date of disease recurrence, or last follow-up. Overall survival (OS) was defined as the time from the date of the start of primary therapy to date of death or the last follow-up.

Statistical analysis

Statistical evaluation was done using SPSS version 25. Baseline demographic and tumor characteristics of TNBC were analyzed. Univariate analysis of prognostic factors was done using the Log Rank test. Co-relation between tumor size and lymph node involvement, upfront surgery and recurrence rates, lymph node status and type of recurrence, and relapses were analyzed. Chi-square test was done to assess the statistical significance of these correlations. Survival estimation was done using the Kaplan Meier method. Multivariate analyses were performed using the Cox regression model. A 'p' value of <0.05 was considered statistically significant.

Results

A total of 457 nonmetastatic breast cancer patients were registered at our institute from January 2014 to August 2018, of which 137 were triple-negative breast cancer (TNBC). This accounted for 29.9% of nonmetastatic breast cancer during this period. 137 patients were eligible for this study as non-metastatic TNBC. The median age at diagnosis was 45 years (20-75). Clinical features including pain, lump, lump with pain, nipple discharge, and lump with ulcers were 19%, 48.9%, 15.3%, 1.5%, and 15.3% respectively. The tumor was right-sided in 49.6% and left-sided in 50.4% at presentation. The median duration of symptoms was 30 weeks (8 – 54). The age group distribution show 20-30 years, 31-40 years, 41-50 years, 51-60 years, 61-70 years, and > 70 years were 13.9%,

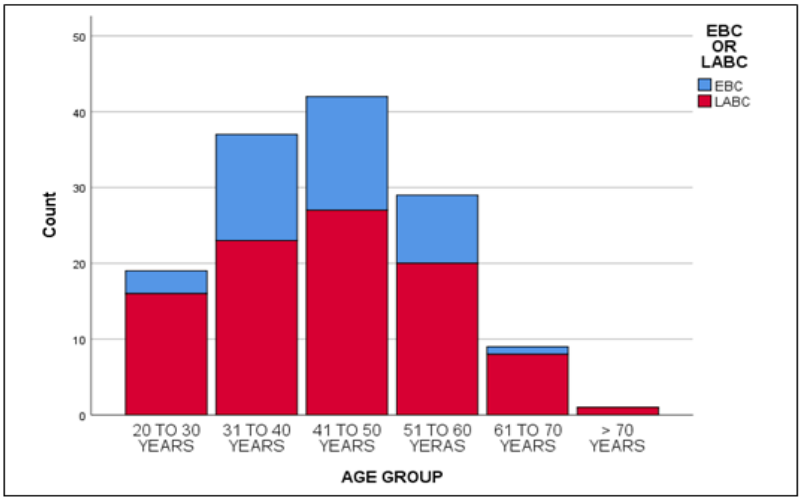


Figure 1. Distribution of Age Group of Patients According to Stage at Diagnosis

Table 1. Comparative Analysis of Different ClinicoPathological Parameters (N=137)

		EBC		LABC		
		Count	N %	Count	N %	p-value
Age < 35	Yes	7	5.1	30	21.9	0.070
	No	35	25.5	65	47.4	
Side	Right	23	16.8	45	32.8	0.425
	Left	19	13.9	50	36.5	
Presenting complains	Pain	13	9.5	13	9.5	0.004
	Lump	23	16.8	44	32.1	
	Lump with pain	5	3.6	16	11.7	
	Nipple discharge	1	0.7	1	0.7	
	Lump with ulcer	0	0.0	21	15.3	
Age Group	20 to 30 years	3	2.2	16	11.7	0.365
	31 to 40 years	14	10.2	23	16.8	
	41 to 50 years	15	10.9	27	19.7	
	51 to 60 years	9	6.6	20	14.6	
	61 to 70 years	1	0.7	8	5.8	
	> 70 years	0	0.0	1	0.7	
Married	Yes	40	29.2	82	59.9	0.123
	No	2	1.5	13	9.5	
Pregnancies	Never	2	1.5	15	10.9	0.071
	One or more	40	29.2	80	58.4	
Breast feeding	Yes	40	29.2	80	58.4	0.071
	No	2	1.5	15	10.9	
NACT	Yes	4	2.9	30	21.9	0.006
	No	38	27.7	65	47.4	
Surgery upfront	Yes	38	27.7	65	47.4	0.006
	No	4	2.9	30	21.9	
Type of surgery	BCS	16	11.7	0	0.0	< 0.001
	MRM	26	19.0	95	69.3	
Nodal status	Positive	19	13.9	65	47.4	0.010
	Negative	23	16.8	30	21.9	
HPE subtype	Cribriform	2	1.5	8	5.8	0.081
	ILC	1	0.7	1	0.7	
	Medullary	4	2.9	1	0.7	
	NOS	35	25.5	85	62.0	
BR grade	Grade I	0	0.0	2	1.5	0.268
	Grade II	17	12.4	27	19.7	
	Grade III	25	18.2	66	48.2	
Pathological T	pT1	3	2.2	2	1.5	< 0.001
	pT2	39	28.5	12	8.8	
	pT3	0	0.0	47	34.3	
	pT4	0	0.0	34	24.8	
Pathological N	pN0	23	16.8	30	21.9	< 0.001
	pN1	19	13.9	14	10.2	
	pN2	0	0.0	37	27.0	
	pN3	0	0.0	14	10.2	

Continued Table 1.

		EBC		LABC		
		Count	N %	Count	N %	p-value
Postopertive stage	Stage IA	3	2.2	0	0.0	< 0.001
	Stage IIA	20	14.6	0	0.0	
	Stage IIB	19	13.9	18	13.1	
	Stage IIIA	0	0.0	33	24.1	
	Stage IIIB	0	0.0	30	21.9	
	Stage IIIC	0	0.0	14	10.2	
LNR group	Not available	2	1.5	9	6.6	< 0.001
	Low risk	29	21.2	29	21.2%	
	Intermediate risk	10	7.3	29	21.2%	
	High risk	1	0.7	28	20.4	
Margin	Negative	42	30.7	93	67.9	0.344
	Positive	0	0.0	2	1.5	
LVI	Negative	10	7.3	6	4.4	0.003
	Positive	32	23.4	89	65.0	
PNI	Negative	21	15.3	24	17.5	0.004
	Positive	21	15.3	71	51.8	
Adjuvant Chetherapy	Yes	42	30.7	93	67.9	0.344
	Not indicated	0	0.0	0	0.0	
	Not taken	0	0.0	2	1.5	
Chemtherpy regimen	AC à T	24	17.5	54	39.4	0.635
	TAC	18	13.1	39	28.5	
	Not taken	0	0.0	2	1.5	
Chest wall RT/ whole breast RT	Yes	37	27.0	89	65.0	0.03
	Not indicated	3	2.2	0	0.0	
	Not taken	2	1.5	6	4.4	
Axilla RT	Yes	37	27.0	89	65.0	0.03
	Not indicated	3	2.2	0	0.0	
	Not taken	2	1.5	6	4.4	
SCF RT	Yes	34	24.8	89	65.0	< 0.001
	Not indicated	6	4.4	0	0.0	
	Not taken	2	1.5	6	4.4	
Site of recurrence	No recurrence	39	28.5	55	40.1	0.007
	Ipsilateral recurrence	1	0.7	4	2.9	
	Lung metastasis	0	0.0	6	4.4	
	Liver metastasis	0	0.0	10	7.3	
	Bone metastasis	0	0.0	2	1.5	
	Brain metastasis	2	1.5	14	10.2	
	Contralaeral metastasis	0	0.0	4	2.9	
Recurrence	Yes	3	2.2	40	29.2	< 0.001
	No	39	28.5	55	40.1	

EBC- early breast cancer; LABC-locally advanced breast cancer; NACT-neoadjuvant chemotherapy; HPE-histopathological examination; BR grade-Bloom-Richardson grade; T- pathological tumor size; N- pathological nodal status; LNR-lymph node ratio; LVI-Lymphovascular invasion; PNI-Perineural invasion; RT-radiation; SCF-supraclavicular; NOS- not otherwise specified

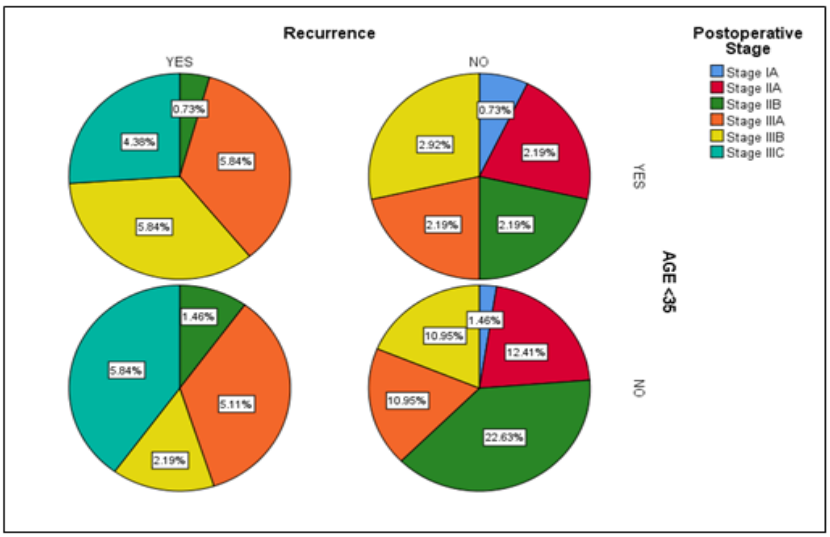


Figure 2. The Recurrence According to Stage and Age Group

27%, 30.7%, 21.2%, 6.6%, and 0.7% respectively. The age group distribution of the patient concern to the stage given in Figure 1. 13.9% of patients were ≤ 35 years of age and 86.1% were > 35 years. The majority of the patients were post-menopausal with 53.3% and 46.7% were premenopausal. The nulliparity and history of breastfeeding were 12.4%, and 87.6% respectively. 10.9% of patients were unmarried and 89.15% of patients were married. The median age at first childbirth was 29 years. Most of the patients were considered for upfront surgery, 75.2% were considered for upfront surgery while 24.8% of patients received neoadjuvant chemotherapy (NACT) followed by surgical intervention. A modified radical mastectomy (MRM) was done in 88.3% of cases and 11.7% underwent breast conservative surgery (BCS). Adjuvant chemotherapy was considered in 98.5% of cases and 1.5% of patients defaulted for adjuvant chemotherapy. Chemotherapy regimen mostly consisted of anthracycline (A) and Cyclophosphamide (C) of 4 cycles followed by taxanes (T) of 4 cycles (4 x AC→4 X T) constituting 56.9% and followed by 6 cycles taxane, anthracycline and Cyclophosphamide (TAC) constituting 41.6% of cases. In the postoperative histopathological report review, it was observed that subtypes of invasive ductal breast

Table 2. Univariate Analysis

Variable		Disease-free Survival (DFS)		Overall Survival (OS)	
		%	p-value	%	p-value
Age <35	Yes	32.5		36.3	
	No	47.8	< 0.001	49.8	< 0.001
Postmenopausal	Yes	48.2		48.3	
	No	36.9	0.003	40.38	0.003
Stage	EBC	51.5		51.5	
	LABC	38.7	< 0.001	40.7	< 0.001
Nodal status	Positive	33.5		38.4	
	Negative	55.3	< 0.001	55.3	< 0.001
LVI	Positive	42.1		43.1	
	Negative	49.5	0.041	50.2	0.020
PNI	Positive	39.6		40.3	
	Negative	48.9	< 0.001	55.5	< 0.01
Pathological T	T1	48.6		49.8	
	T2	46.4		45.4	
	T3	41.4	0.023	44.5	0.002
	T4	32.2		33.9	
Pathological N	N0	55.5		55.5	
	N1	41.0		40.8	
	N2	31.9	< 0.001	37.8	< 0.001
	N3	22.2		32.5	

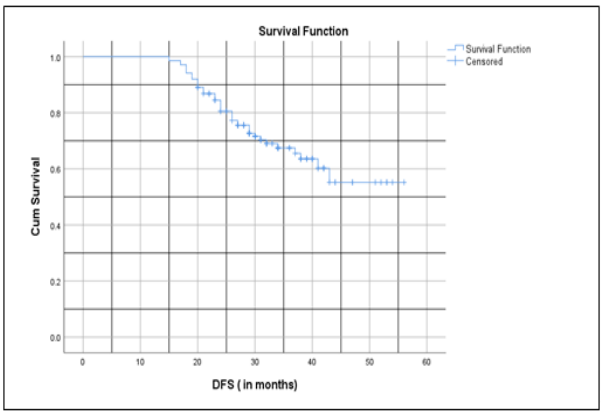


Figure 3A. The Cumulative Disease-free Survival Kaplan-Meier Curve

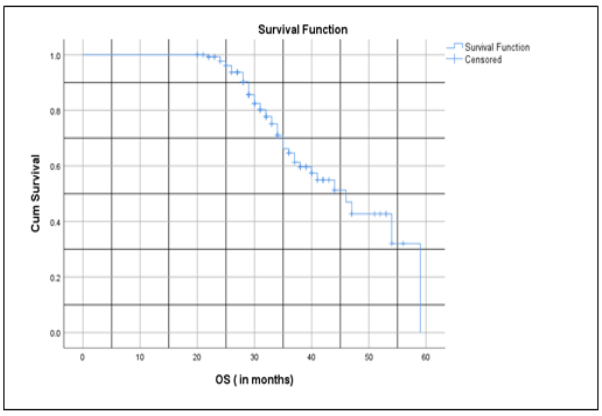


Figure 3B. The cumulative overall survival Kaplan-Meier Curve

carcinoma were not otherwise specified (NOS), cribriform, medullary and invasive lobular carcinoma as 87.6%, 7.3%, 3.6% and 1.5% respectively. The grading of the tumors were grade I, grade II, and grade III as 1.5%, 32.1% and 66.4% respectively of the tumors. Pathologically tumor size T1, T2, T3 and T4 were 3.6%, 37.2%, 34.3% and 24.8% respectively. The pathological nodal status of the tumors was N0, N1, N2 and, N3 as 38.7%, 24.1%, 27%, and 10.2% respectively. The lymph node positivity was statistically significantly associated with large tumor size (p=0.040), but not statistically significantly associated with LVI (p=0.074), PNI (p=0.139) and higher tumor grade (p=0.765). The median total number of lymph nodes removed during surgical intervention was nine (9) and the median number of positive lymph nodes was two (2). Lymph node ratio (LNR) was calculated as the ratio of the number of positive lymph nodes to the total number of lymph nodes removed during surgical intervention. The median LNR was 0.25 (0.00 – 1.00). LNR was not available in 8.02% (11) of patients as there were no pathologically identifiable nodal tissues were found in the postoperative specimen. Patients were classified as low risk, intermediate-risk, and high risk based on LNR. Patients with LNR 0.00-0.20, 0.21-0.65, and > 0.65 were defined as low risk, intermediate-risk, and high risk respectively. LNR with low risk, intermediate risk, high risk, and not available were in 42.3%, 28.5%, 21.2%, and 8.02% respectively. Overall 61.3% of patients presented with node-positive disease while 38.7% presented with node-negative disease. Early breast cancer was seen in 30.7% and locally advanced breast cancer was observed in 69.3% of cases. Postoperative staging shows that stage IA, IIA, IIB, IIIA, IIIB, and IIIC were 2.2%, 14.6%, 27%, 24.1%, 21.9% and 10.2% respectively. Lymphovascular invasion (LVI), perineural invasion (PNI), and margin positive were observed in 88.3%, 67.2%, and 1.5% respectively. Adjuvant radiation was indicated in 97.8% of cases, but taken by 92% of patients and adjuvant radiation was defaulted by 5.8% of cases. Twenty-nine percent of patients show recurrences at a median follow up of 38 months. Brain was the most common site of recurrence with 37.2%, liver 23.2%, lung 13.9%, ipsilateral 11.6%, contralateral metastasis 9.3% and bone 4.6% respectively. Comparative analysis of different clinicopathological parameters presented in Table 1. Recurrence was statistically significantly correlating

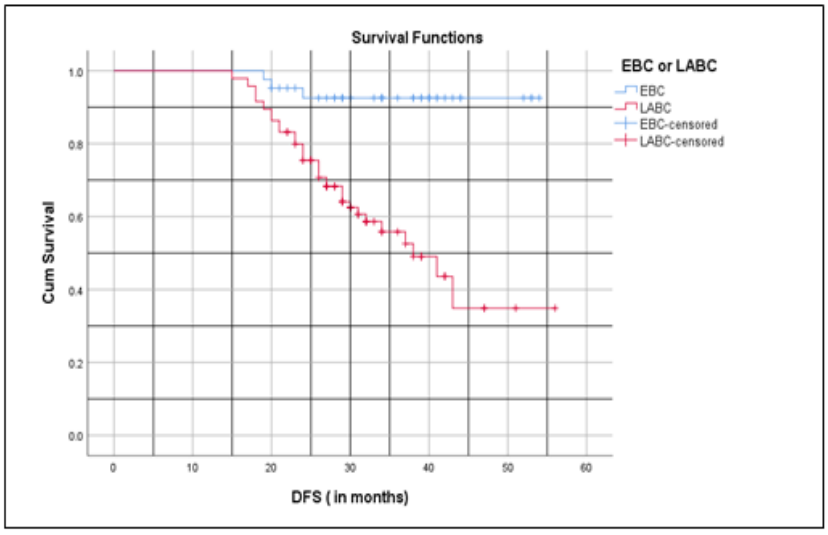


Figure 4. Disease-free Survival (DFS) in Months Comparing to Stage (EBC Vs LABC); Log rank p= < 0.001

with age at presentation (p=0.019; nominal by interval; Eta=0.309), age ≤ 35 (p= < 0.001), pathological N status (p= < 0.001), pathological stage (p= < 0.001), nodal status at diagnosis (p= < 0.001), PNI (p= < 0.001), number of positive lymph nodes (p= < 0.001), and LNR (p= < 0.001). Recurrence was not correlating statistically significantly with pathological T status (p=0.084), LVI (p=0.083), grade (p=0.58), and total number of lymph nodes removed (p=0.32). The recurrence according to stage and age group represented as in Figure 2. The median DFS was not reached but mean DFS was 43.6 months (95% CI; 40.58 – 46.72). The median OS was 46 months (95% CI; 39.1 – 52.8). Three-year DFS and OS were 65.5% and 66.2 % respectively. The Kaplan-Meier estimate of survival for DFS (Figure 3A) and OS is represented in (Figure 3B). The 3-year DFS for patients with EBC and LABC was 92.5% and 55.8% respectively (p= < 0.001), the Kaplan-Meier survival curve is represented in Figure 4. In univariate analysis age ≤ 35, stage, nodal status, pathological T status, and pathological N status, have a significant impact on DFS and OS given in the Table 2.

Discussion

TNBC is known for its heterogeneity and early recurrence. One of the important things to consider in TNBC is that the ineffectiveness of the therapies targeted against ER, PR, and Her2neu receptors. Patients expressing these receptors having different therapeutic strategies due to the available number of anti-targeted agents. Therefore, the non-TNBCs have a good prognosis in comparison to TNBC. When TNBCs diagnosed earlier and treated adequately, the survival rates are comparable to non-TNBCs [13]. In this study TNBC accounted for 29.9% of non-metastatic breast cancer. Studies by Indian authors have reported a wide range of TNBCs from 11.8% to 31.9% [14-15]. Sarin et al. reported an incidence of 20%, similarly Chintalapani et al. reported an incidence of 19.3% of TNBC [16-17]. Murtaza et al. reported TNBC incidence in their study as 43.5% [18]. In our study the median age at presentation was 45 years which was similar to other studies as Lakshmaiah et al. and Suresh et al. the median age in their studies were 45 years and 49 years respectively [19-20]. Previous reports have also suggested a younger age at diagnosis in TNBCs (Hudis and Gianni, 2011; Sen et al., 2012). The median age at presentation in the Western population in a study was 53 years [21]. In this study the most commonly involved age group was 41-50 years with 30.7% followed by 31-40 years with 27%. A study by Chowdhary et al. of 185 TNBC patients, almost reported the similar findings [22]. In this study the tumor was right-sided in 49.6% and left-sided in 50.4% at presentation. Doval et al. in their study of 148 patients found 53.45% right-sided and left-sided in 46.6% [23]. In our study the majority of the patient were postmenopausal 53.3% which was similar to that of a study by Chintalapani et al. in their study 56.6% of patients were postmenopausal while Lakshmaiah et al. reported 40.47% of postmenopausal among the analysis of 84 patients [19]. A study by Doval et al. shows postmenopausal patients with 69.9%, which is higher than our study [23]. These studies suggest that the hormonal status of the patient in the postmenopausal state may have a role in the tumor growth or angiogenesis (Demicheli et al., 2004). In this study most of the patients (75.2%) underwent upfront surgical intervention and the rest of 24.8% were considered for NACT followed by surgical intervention. In this study MRM was the main surgical intervention followed by BCS similar reports were also found in other Indian studies [17, 24-19]. The type of surgical procedure depends on the extent of the presenting disease, patient's preference, and access to tertiary health care center. In this study majority of the patient were pathological stage III (56.2%) and grade III (66.4%). Indian literature regarding TNBC also reported similar findings as most of the TNBC presented with stage III [25, 23-19]. In this study the pathological T2 (37.2%) was the most common finding followed by T3 (34.3%), similar findings were reported by Lakshmaiah et al. in their study with pathological T2 (35.7%), Hakim A, et al. in their study also reported pathological T2 (31.4%) [26], while Doval et al. reported pathological T2 (62.1%) in their study which was not consistent with our study [23]. In our study majority (61.3%) of patients presented with node-positive almost similar findings were reported by Lakshmaiah et al. in their study with 63% node-positive. Other Indian studies reported axillary node positivity in their studies from 50% to 74% [27, 18, 28] while Doval et al. reported 36.8% node-positive in their study [23], which was not consistent with our study. In our study 30.7% of patients were EBC and 69.3% were LABC. A study by Suhani et al. reported 56.1% of patients of TNBC presented as LABC [29]. Most of the Indian studies reported the presentation of LABC from 35% to 60% [18, 26-23-19]. The recurrence rate in this study was 29.2% at the median follow-up of 38 months. In this study the brain was the most common site of recurrence followed by liver and lung in TNBCs. Rathi et al. in their study reported lungs as the most common site of recurrence [28]. The mean DFS and OS were 43.6 and 46 months respectively. Three-year DFS and OS were 65.5% and 66.2% respectively. Rathi et al. reported 74.2% of 3-year DFS while Suresh et al. and Sarin et al. reported 3-years DFS more than 80% [28, 23-16]. The data from Chinese studies reported DFS and OS 77.8% and 79.9% [30]. A study from the USA reported a 3-year RFS of 63% and an OS of 71% [31]. These data reveals wide variability of survival outcomes around the regions of the world. This may be due to stage at presentation and survival analysis without stage IV disease etc. In our study the lower DFS may be due to a higher percentage of patients with LABC compared to other Indian studies on TNBC. The survival was better in EBC compared to LABC. The survival analysis revealed that better DFS and OS are significantly associated with EBC. The patients with EBC were managed with surgical intervention followed by adjuvant systemic chemotherapy and radiotherapy (when indicated) to reduce the risk of recurrence. Those patients presented with LABC, the majority of them were managed with NACT followed

by surgery and adjuvant chemotherapy and radiotherapy. Axillary lymph node involvement results in poor DFS and OS which is statistically significant. This node involvement is well known prognostic factor in breast cancer that can predict the recurrence. The result of this study is per other studies (Tian et al. 2008; Ovcaricek et al., 2011). The pathological feature LVI did not influence DFS or OS but PNI was associated with poor DFS and OS with statistical significance. TNBC responds well to anthracycline and taxane-based systemic chemotherapy, which provide good response to treatment, though it may result in early recurrence [32-33].

In conclusion, triple-negative breast cancers constitute a significant proportion of breast cancer which is ER-negative, PR-negative, and Her2neu negative. They are high-grade tumors mostly presented in locally advanced stages and most of the patients are young. Locally advanced TNBCs are clinically more aggressive than early breast cancers. TNBCs are clinically aggressive with high risk of metastasis to visceral organs compared to non-TNBCs. However TNBCs respond well to systemic chemotherapy, thus better and less toxic management options to be considered along with there is also a need for newer targeted therapy. The survival of TNBCs in the Indian scenario is less in comparison to the Western population, probably due to racial factors, socioeconomic factors and health care access facility. The present study has a limitation of selection bias which may be due to retrospective nature.

Financial support and sponsorship

Nil

Acknowledgments

We acknowledge the help extended by the Department of General Surgery, Institute of Post Graduate Medical Education and Research, Kolkata, India.

Conflicts of Interest

The authors have no conflicts of interest to declare.

References

1. World Health Organization. Global Health Observatory. Geneva: World Health Organization; 2018. Available from http://gco.iarc.fr/
2. Globocan India 2018. Population fact sheets p. 1-2. Available from http://www.gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf
3. Ahmedin Jemal, DVM, Ph.D.; Freddie Bray, Ph.D.; Melissa M. Center, MPH; Jacques Ferlay, ME; Elizabeth Ward, Ph.D. Global Cancer Statistics; CA Cancer J Clin 2011;61:69–90.; DOI:10.3322/caac.20107
4. Idil Cetin, Mehmet Topcul; Triple Negative Breast Cancer; Asian Pac J Cancer Prev, 15 (6), 2427-2431; DOI:http://dx.doi.org/10.7314/APJCP.2014.15.6.2427
5. William D. Foulkes, M.B., B.S., Ph.D., Ian E. Smith, M.D., Jorge S. Reis-Filho, M.D., Ph.D.; Triple-Negative Breast Cancer; N Engl J Med 2010;363:1938-48.; DOI: 10.1056/NEJMra1001389.
6. Sattar HA. Female Genital System and Breast. In: Kumar V, Abbas AK, Aster JC. Robbins Basic Pathology. 9th Eds. Philadelphia, Elsevier 2013. Pp. 681-714.
7. Hashmi AA, Edhi MM, Naqvi H, Faridi N, Khurshid A, Khan M. Clinicopathological features of triple-negative breast cancers: An experience from Pakistan. Diagn Pathol. 2014;9:43.
8. T. Sørlie, C. M. Perou, and R. Tibshirani, "Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications," Proceedings of the National Academy of Sciences of the United States of America,vol. 98,no.19,pp.10869–10874, 2001.
9. T. Sørlie, R. Tibshirani, and J. Parker, "Repeated observation of breast tumor subtypes in independent gene expression data sets," Proceedings of the National Academy of Sciences of the United States of America, vol.100,pp.8418–8423,2003.
10. N. U. Lin, A. Vanderplas, M. E. Hughes et al., "Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network," Cancer, vol.118,no.22,pp.5463–5472,2012.
11. Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de, Vijver MJ, eds. WHO classification of tumors of the breast, 4 edn. Geneva: World Health Organization 2012
12. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer I. The value of histological grade in breast cancer: Experience from a large study with long-term follow-up. Histopathology 1991;19:403-10.
13. Schwentner L, Wolters R, Koretz K, Wischnewsky MB, Kreienberg R, Rottscholl R, et al. Triple-negative breast cancer: The impact of guideline-adherent adjuvant treatment on survival – A retrospective multi-center cohort study. Breast Cancer Res Treat 2012;132:1073-80
14. Sharma B, Satyanarayan, Kalwar A, Sharma N, Kapoor A, Kumar N. Five year retrospective survival analysis of triple-negative breast cancer in North-West India. Indian J Cancer 2013;50:330-2.
15. Sharma M, Sharma JD, Sarma A, Ahmed S, Kataki AC, Saxena R, et al.Triple negative breast cancer in people of North East India: Critical insights gained at a regional cancer center. Asian Pac J Cancer Prev 2014;15:4507-11
16. Sarin R, Khandrika L, Hanitha R, Avula A, Batra M, Kaul S, et al. Epidemiological and survival analysis of triple-negative breast cancer cases in a retrospective multicenter study male breast cancer: Epidemiological data from the North of Peru. Indian J Cancer 2016;53:353-9.
17. Chintalapani SR, Bala S, Konatam ML, Gundeti S, Kuruva SP, Hui M. Triple-negative breast cancer: Pattern of recurrence and survival outcomes. Indian J Med Paediatr Oncol 2019;40:67-72.
18. Murtaza Akhtar, Subhrajit Dasgupta, Murtuza Rangwala; Triple-negative breast cancer: An Indian perspective. Breast Cancer: Targets and Therapy 2015:7 239–243; http://dx.doi.org/10.2147/BCTT.S85442
19. Lakshmaiah KC, Das U, Suresh TM, Lokanatha D, Babu GK, Jacob LA, et al. A study of triple-negative breast cancer at a tertiary cancer care center in Southern India. Ann Med Health Sci Res 2014;4:933-7.
20. Suresh P, Batra U, Doval DC. Epidemiological and clinical profile of triple-negative breast cancer at a cancer hospital in North India. Indian J Med Paediatr Oncol 2013;34:89-95.
21. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, et al. Triple-negative breast cancer: Clinical features and patterns of recurrence. Clin Cancer Res 2007;13(15 Pt 1):4429-34.
22. G. S. Chowdhary, Sarthak Mishra; An analysis of incidence and prevalence and prognostic outcomes for women with triple-negative breast cancer in an Indian setting;

International Journal of scientific research; Volume-8 | Issue-12 | December - 2019 | PRINT ISSN No. 2277 - 8179 | DOI: 10.36106/ijsr
23. Dinesh Chandra Doval, P Suresh, Rupal Sinha, Saud Azam, Vineet Talwar, Kapil Kumar, Anurag Mehta, Ullas Batra; Eight Year Survival Analysis of Patients with Triple Negative Breast Cancer in India; Asian Pacific Journal of Cancer Prevention, Vol 17, 2016; Asian Pac J Cancer Prev, 17 (6), 2995-2999
24. Satyanarayan V. and Ashok Akula, "Triple-negative breast cancer- experience at a tertiary care center, South India" International Journal of Current Research, 8, (11), 42382-42383.
25. Prabu MP, Raina V, Shukla NK, Mohanti BK, Deo SV. A study of triple-negative breast cancer at a Cancer Institute in India. J Clin Oncol 2011;29:15. [Suppl; Abstr e11548].
26. Hakim A et al. (2019), Epidemiology of Breast Cancer in a Single Institute in North India with High Incidence of Triple-Negative Breast Cancers. Int J Ped & Neo Heal.3:1, 27-31.
27. G M Reddy, Pooja K Suresh, R R Pai; Clinicopathological features of triple-negative breast carcinoma; Journal of Clinical and Diagnostic Research. 2017 Jan, Vol-11(1): EC05-EC08; DOI: 10.7860/JCDR/2017/21452.9187
28. Deepak Kumar Rathi, S Chaudhary, M Sharma, et al. " Incidence and Clinical Profile of Triple-Negative Breast Cancer (TNBC)."IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 17, no. 1, 2018, pp. 04-06; DOI: 10.9790/0853-1701100406
29. Suhani, Parshad R, Kazi M, Seenu V, Mathur S, Dattagupta S, et al. Triple-negative breast cancers: Are they always different from non-triple-negative breast cancers? An experience from a tertiary center in India. Indian J Cancer 2017;54;658-63.
30. Li CY, Zhang S, Zhang XB, et al (2013). Clinicopathological and prognostic characteristics of triple-negative breast cancer (TNBC) in Chinese patients: a retrospective study. Asian Pac J Cancer Prev, 14, 3779-84.
31. Dawood S, Broglio K, Kau SW, et al (2009). Triple receptor negative breast cancer: the effect of race on response to primary systemic treatment and survival outcomes.J Clin Oncol, 27, 220-6
32. Liedke C, Mazouni C, Hess KR, et al (2008). Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol, 26, 1275-81.
33. Keam B, Im SA, Kim HJ, et al (2007). Prognostic impact of clinicopathological parameters in stage II/III breast cancer treated with neoadjuvant docetaxel and doxorubicin chemotherapy: paradoxical features of the triple-negative breast cancer. BMC Cancer, 7, 203.

DOI:10.31557/APJCC.2020.5.2.95

RESEARCH ARTICLE

Symptom and Anxiety Assessment in Gynecologic Cancer Patients Receiving Chemotherapy

Pongsaton Viriyasiri, Phatthanan Phutthikiat, Phatthawan Phonmak, Phurinut Krutjaikla, Sittichai Ongtip, Prapaporn Suprasert

Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Thailand.

Abstract

Background: Side effects of chemotherapy usually disturbed the daily life of patients. During chemotherapy, quality of life of patients is affected by the severity of symptoms experienced. **Objective:** To evaluate the side effects experienced by gynecologic cancer patients receiving chemotherapy. **Methods:** Gynecologic cancer patients receiving chemotherapy (at least 1 cycle with standard premedication that included antiemetic drugs) between 18 June and 25 September 2019 were invited to this study. Participants were interviewed by our team for personal data and attitudes toward their disease and treatment. In addition, the Edmonton Symptom Assessment System (ESAS-Thai version) tool, and Multinational Association for Supportive Care in Cancer (MASCC) antiemetic tool were used to assess the symptoms during chemotherapy. **Results:** One hundred sixty-five participants entered this study. The mean age was 53.5. The three most common type of cancer were ovarian (37.6%), cervical (37.6%) and uterine cancer (21.8%). Most common chemotherapy was carboplatin plus paclitaxel (64.8%). Two-thirds of the participants believed they could be cured. The most common severe symptom from the ESAS tool was pain (20.6%), followed by fatigue (18.8%), appetite change (16.4%) and numbness (10.3%). In addition, 10.9% of patients experienced nausea/vomiting in acute phase, while 20.6% experienced it in the delayed phase. **Conclusion:** Our participants revealed positive attitudes toward cancer and treatment. Some patients experienced nausea and vomiting despite using antiemetic drugs. The most frequent self-reported symptom was pain. Therefore, pain control was necessary to improve their quality of life.

Keywords: Chemotherapy- gynecologic cancer- CINV- symptom assessment- ESAS- MASCC antiemetic tool

Asian Pac J Cancer Care, **5 (2)**, 95-100

Submission Date: 02/26/2020 Acceptance Date: 05/05/2020

Introduction

Chemotherapy is one of the main treatments in gynecologic cancer especially in advanced stages and recurrences. Various regimens such as Carboplatin plus Paclitaxel, Cisplatin plus 5 –Fluorouracil, Gemcitabine, etc. are frequently used [1]. It is known that these chemotherapy regimens cause many side effects like nausea and vomiting, anemia, neutropenia, numbness, etc. Both chemotherapy side effects and the symptoms of the cancer negatively impact the quality of life of the patients. Akin and Durna [2] conducted a comparative study of the symptoms occurring after receiving chemotherapy by using the Edmonton Symptom Assessment System (ESAS) in 119 patients receiving chemotherapy. The authors compared the ESAS answers among patients, family caregivers and nurses and reported that the most frequent severe symptoms were tiredness, loss of well-being, anxiety, drowsiness, appetite change, depression, pain and nausea. In addition, the authors summarized that the patients and caregivers demonstrated a strong agreement regarding symptoms in contrast with patients and nurses that showed poor to fair agreement. Therefore, self-assessment by patients was important. Regarding gynecologic cancer, Nazik et al [3] studied anxiety and symptoms in Turkish gynecologic cancer patients receiving chemotherapy by using the ESAS and the State-Trait Inventory. They found that the average highest point of symptom was fatigue while the level of anxiety was moderate. Furthermore, chemotherapy-induced nausea and vomiting (CINV)

Corresponding Author:
Dr. Prapaporn Suprasert
Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Thailand.
Email: psuprase@gmail.com

was mentioned as one of the adverse events that affected the daily life of patients [4]. However, the data of the symptoms including CINV assessed by the patients in Thailand is still limited. Therefore, we conducted this study to evaluate these aspects of our gynecologic cancer patients during chemotherapy. We hope that the outcome should be beneficial for health-care providers to improve quality of life of those patients.

Materials and Methods

Study design

This study was designed as a cross-sectional survey and approved by the Research Ethics Committee 4, Faculty of Medicine, and Chiang Mai University. The study code is OBG-2562-06369.

Patient selection

The gynecologic cancer patients who received chemotherapy (at least 1 cycle) at the Gynecologic Oncology Unit, Chiang Mai University Hospital from 18 June 2019 to 25 September 2019 and were able to communicate in Thai were invited to participate in this study. The patients whose performance status was poor (ECOG criteria more than 3), unable to interview, or revealed a symptom of nausea / vomiting from other causes besides chemotherapy were not invited in this project. All patients received standard premedication that consisted of lorazepam, serotonin antagonist, dexamethasone and anti-histamine about 30 minutes before initiated chemotherapy.

Instruments

The data were collected using 3 parts of case record form consisting of patient data form, ESAS (Thai version) form [5], and Multinational Association for Supportive Care in Cancer (MASCC) antiemetic tool (MAT) form [6].

The patient data form includes of the demographic data, gynecologic cancer data and the attitude of the patient to their disease and treatment outcome. The ESAS scale was developed by Eduardo Bruera in 1991 with the purpose to improve patient care in oncology by evaluating patient's opinion about the severity of his/her symptoms [7]. The ESAS evaluates nine common symptoms in patients with cancer: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite change, loss of well-being and shortness of breath. However, patients could report other problems in this instrument. The severity of each symptom was rated on a numerical scale from 0 to 10, with 10 meaning the worst severity. After that, the score was categorized to 4 levels; no symptom if score equaled to 0, mild if the score was in a range of 1-3 scores, moderate if the score was in a range of 4-6 scores and severe if the score was more than 7 scores [7]. In this study, we used ESAS Thai version that was validated with the original [5].

The third part of the data collection is the MAT. The MAT was first created and posted in 2004 by members MASCC of to assist patients and oncology professionals in communicating accurately about nausea and vomiting that may occur with chemotherapy. We used this tool by translating to Thai language to evaluate nausea and / or vomiting of the patients. The definition of vomiting was the bringing up of stomach contents and the definition of nausea was the feeling that you might vomit. The patients were asked about nausea and vomiting during the first 24 hours and at day 2 to day 4 after receiving the former chemotherapy. If vomiting was present, the patients were asked how many times it happened while if the nausea was presented, the patients were asked how much nausea was experienced during the first 24 hours and at day 2 to day 4. Nausea and/or vomiting that occurred during 24 hours were classified as acute phase whereas the nausea and/or vomiting that occurred after that (day 2 - day 4) were classified as delayed phase.

The participants were interviewed face to face by our investigator team during waiting to see the doctors at out-patient-department of gynecologic oncology unit for the next course of chemotherapy. The interview time was about 20 minutes. The medical information of each participant was obtained from electronic patients files.

Statistical analysis

The sample size for this study was estimated from the data of a previous study. The study revealed fatigue as the most frequent symptom which was found in 90% of 41 participants [3]. The 95 inter-percentile reference intervals for calculation accommodated the possibility of a loss of follow up participants. Thus, this study required to enroll about 160 participants.

The statistical analysis of the data was conducted using the IBM SPSS Statistics for Windows program (version 22). Descriptive statistics were used to summarize patient characteristics. Chi-square or Fisher's Extract test was used for comparative analysis of the factors between acute and delayed nausea and vomiting. A p-value of < 0.05 was suggested statistically significant.

Results

There were 165 participants entered to the present study. The clinical data was noted in Table 1. The mean age was 53.4. Over 90% were Thai. About two-thirds of the participants were married and about 75% had children. Only 14.5% of the participants were government service. Nearly 70% of participants did not finish high school. The majority of our participants had an income of less than 10,000 baht per month (about 331 US dollars). Around 63% of the participants did not have any underlying disease. Regarding drug abuse, the participants revealed alcohol addicted, cannabis used and smoking at 6.1%, 3.0%, and 2.4%, respectively. The top three-cancer types were ovarian, cervical and uterine cancer and nearly 60% were in stages 3 and 4. The most common chemotherapy regimen was carboplatin plus paclitaxel. 62.4% of the participants were undergoing chemotherapy for the first time and about 70% had experienced more than 1 cycle at the interview time.

Regarding attitude to their cancer, nearly 60% of the participants believed that they could be cured but it took a long time while 24% believed that it was not to be

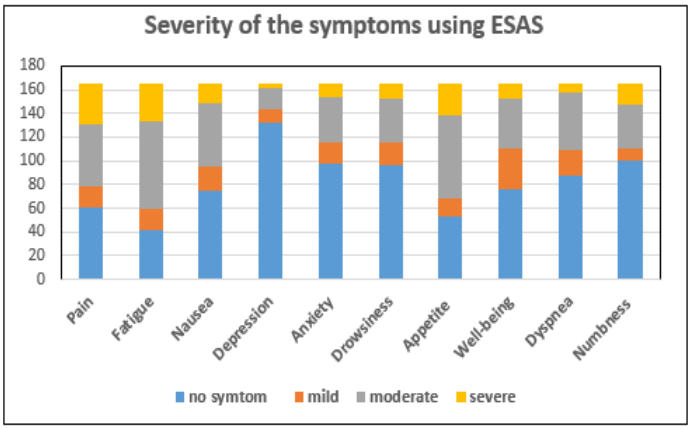
Table 1. Distribution of Clinical Data Related to Gynecologic Cancer Patients

	N (%)
Mean age + SD (year)	53.4 (12.8)
Race	
Thai	149 (90.3)
Others	16 (9.7)
Status	
Single	32 (19.4)
Married	111 (67.3)
Divorce	6 (3.6)
Widow	16 (9.7)
Number of children	
0	42 (25.5)
1	37 (22.4)
2	63 (38.2)
3	15 (9.1)
>3	8 (4.6)
Occupation	
Government service	24 (14.5)
State enterprise	1 (0.6)
Merchant	16 (9.7)
Employment	24 (14.5)
Owner	6 (3.6)
Others	94 (57)
Education	
Undergraduate	115 (69.7)
Bachelor degree	44 (26.7)
Postgraduate	6 (3.6)
Income (per month: Baht)	
<10,000	109 (66.1)
10,000-20,000	24 (14.5)
20,000-30,000	12 (7.3)
>30,000	20 (12.1)
No underlying disease	105 (63.6)
Cannabis used	5 (3.0)
Alcohol addicted	10 (6.1)
Smoking	4 (2.4)
Gynecologic cancer type	
Ovary	62 (37.6)
Cervix	47 (28.5)
Corpus	36 (21.8)
Fallopian tube	10 (6.1)
Gestational Trophoblastic Neoplasia	8 (4.8)
Primary peritoneum	1 (0.6)
Vagina	1 (0.6)
Stage	
I	35 (21.2)
II	28 (17.0)
III	74 (44.8)
IV	28 (17.0)
Chemotherapy	
Carboplatin plus Paclitaxel	107 (64.8)
Cisplatin plus 5 –Fluorouracil	10 (6.1)
Gemcitabine	8 (4.8)
Weekly Paclitaxel	5 (3.0)
Others	35 (21.2)
Chemo naive	103 (62.4)
Current cycle of chemotherapy	
1	45 (27.3)
2	29 (17.6)
3	20 (12.1)
4	21 (12.7)
5	15 (9.1)
6	32 (19.4)
>6	3 (1.8)
Phase of treatment	
3-12 months	105 (63.6)
>12 months	60 (36.4)

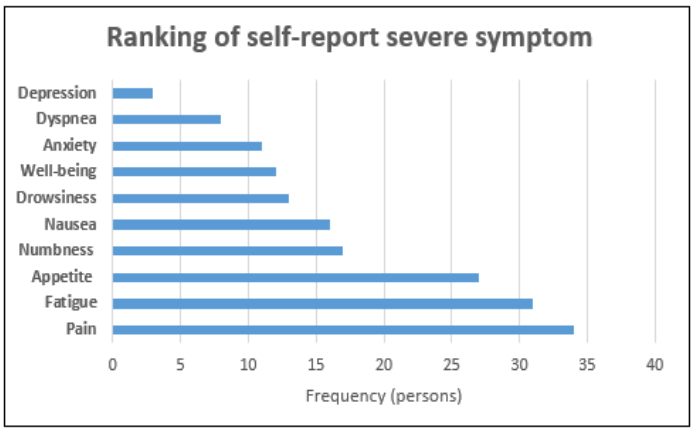
cured. Concerning the attitude of chemotherapy, over 90% believed that chemotherapy could cure cancer and half of them were concerned about the side effect. Interestingly, there was no significant difference between the line of chemotherapy and the patients' attitude of cancer as presented in Table 2.

About the ESAS outcome, Figure 1A and 1B showed the number of patients categorized by the degree of each symptom and the rank of severity of symptoms. The numbness was the symptom that patients frequently complained about. Thus, we included this symptom in part of the interview later. 20.6% of the patients identified pain as the most frequent severe symptom, fatigue (18.8%), appetite change (16.4%) and numbness (10.3%). Regarding severe numbness in 16 patients, the most two frequent chemotherapy regimens were Carboplatin plus Paclitaxel (9 cases) and Cisplatin plus 5-Fluorouracil (4 cases).

Concerning CINV from the participants' view, in the acute phase, 18.2% experienced vomiting with the median episode at 2 (range 1-8) times and 25.5% experienced nausea with a median scale at 3.5 (range 1-8). Moreover, in delayed phases, 26.1% experienced vomiting with the median episode at 3 (range of 1-10) times and 45.5% experienced nausea with the median scale at 5 (range 1-10). Table 3 showed the relation between CINV in acute and delayed phases and found that there was a significant difference in both phases. Patients who experienced vomiting and/or nausea in both acute and delayed phases were 10.9% and 20.6%, respectively.



1A, Severity of the Symptoms Divided to Four Levels



1B, Ranking of Self-report Severe Symptom

Figure 1. Self- assessment Using the Edmonton Symptom Assessment System (ESAS)

Discussion

This study revealed a positive attitude to cancer from our participants. Over 90% of the chemonaive and recurrent setting believed that their cancer was cured with chemotherapy. This was unlike the following report by Badihian et al.[8] who conducted a cross-sectional survey among 953 non-institutionalized individuals in Isfahan, Iran from November 2014 to February 2015 and found about one-third of participants agreed that it is very hard to regain health after a diagnosis of cancer even when treated with highly developed medical science. However, our data came from the participants who developed cancer and still received chemotherapy with the hope to cure. It was noticed that about 3% of our participants used cannabis during chemotherapy with the reason to help them sleep. The benefits and harms of cannabis to cancer are inconclusive due to inconsistent findings and lacked well design evidence [9].

Regarding CINV, one-third of the participants revealed vomiting and half of the participant's revealed nausea that occurred in the acute and/or delayed phase. Despite

Table 2. Attitude to Cancer Divided by Chemotherapy Status (N=165)

	Chemotherapy status (N)		Total	P value
Disease	First line (%)	Beyond first line (%)		
The disease could not be cure	24 (14.5)	16 (9.7)	40 (24.2)	0.258*
The disease took a long time to cure	57 (34.5)	39 (23.6)	96 (58.2)	
The disease was easy to cure	22 (13.3)	7 (4.2)	29 (17.6)	
Total	103 (62.4)	62 (37.6)	165 (100)	
Chemotherapy				
It cured cancer	43 (26.1)	24 (14.5)	67 (40.6)	0.197#
It cured cancer with side effect	57 (34.5)	32 (19.4)	89 (53.9)	
It cannot cure cancer	3 (1.8)	6 (3.6)	9 (5.5)	
Total	103 (62.4)	62 (37.6)	165 (100)	

*Chi-square test; #Fisher exact test

Table 3. The relation between Acute and Delayed Phase of Nausea and Vomiting

Acute phase	Delayed phase		Total	P value*
	Yes (%)	No (%)		
Vomiting				<0.001
Yes	18 (10.9)	12 (7.3)	30 (18.2)	
No	25 (15.2)	110 (66.7)	135 (81.8)	
Total	43 (26.1)	122 (73.9)	165 (100)	
Nausea				<0.001
Yes	34 (20.6)	8 (4.8)	42 (25.5)	
No	41 (24.8)	82 (49.7)	123 (74.5)	
Total	75 (45.5)	90 (54.5)	165 (100)	

*Chi-square test

the antiemetic drugs, CINV still occurred. However, our result was similar to the previous study from Hsieh et al [10]. They studied the incidence of CINV after highly or moderately emetogenic chemotherapy for cancer in over 600 patients from 6 Asia Pacific countries using MASCC antiemetic tool like us. The authors reported emesis and nausea was observed in 30% and 50% both acute and delayed phase, respectively. They also found that physicians tended to underestimate the nausea rate especially in the delayed phase but overestimated emesis incidence. The underestimation of nausea was still the problem and it was difficult to control with standard antiemetic drug like serotonin-antagonist [11]. CINV was associated with a negative effect on daily life including effects on food intake, weight loss, effects on social interaction, dehydration, difficulty with sleeping and anxiety [4].

Concerning self-assessment with the ESAS system, our study found the most frequent severe symptom was pain followed by fatigue, appetite change, and numbness. This finding was different from Nazik et al [3]. The authors using the ESAS tool for assessment 41 Turkish gynecologic cancer patients receiving chemotherapy at least 3 cycles and showed the most frequent severe symptom was fatigue followed by drowsiness, depression, and pain. The difference might be from the distinction of nationality and the number of participants. However, all severe symptoms that disturbed participants were reversible except numbness. In our study, numbness was the symptom that we included later due to many patients complaints about this symptom in the initial phase of the survey. Hence, the rate of severe numbness in our study was underestimated. Numbness is one kind of neurotoxicity frequently developed form receiving cisplatin and paclitaxel and no effective treatment to improve [12].

The strength of the present study was a sufficient number of participants in one institution. Thus, the guideline of treatment was similar. In addition, our study was interviewed by well-trained interviewers. Thus, the data was more reliable than the participants self -report. However, this study recruited about one-fourth of the participants who just received only 1 cycle of chemotherapy. Therefore, they might not be represented as cumulative symptoms.

For future research, we recommended conducting the study with in more specific chemotherapy regimens. Accordingly, the management of side-effects in a specific regimen could be improved.

In conclusion, our patients revealed a positive aspect to cancer and treatment. A part of patients still observed nausea and vomiting even using the anti-emesis drugs. The most frequent self- report symptom was pain. Hence, pain control should be a significant part of any treatment in order to improve quality of life.

Acknowledgements

We received the funding from Faculty of Medicine, Chiang Mai University. We would like to thanks the nurses at Outpatient Department and Oncologic site at Maharaj Nakorn Chiang Mai Hospital; Miss Sukanya Yanunto, Miss Sopida Fanchomphu and Miss Orathai Baisai for their supports and Chiang Mai University English Language Team (CELT) consultant for providing language help.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

References

1. NCCN Clinical Practice Guidelines in Oncology; 2019 [2019 Dec 31]. Available from: https://www.nccn.org/store/Profile/Profile.aspx?requiredid =1
2. Akin S, Durna Z. A comparative descriptive study examining the perceptions of cancer patients, family caregivers, and nurses on patient symptom severity in Turkey. Eur J Oncol Nurs 2013;17:30-7.
3. Nazik E, Arslan S, Nazik H, Narin MA, Karlangic H, Koc Z. Anxiety and symptom assessment in Turkish gynecologic cancer patients receiving chemotherapy. Asian Pac J Cancer Prev. 2012;13:3129-33.
4. Salihah N, Mazlan N, Lua PL. Chemotherapy-induced nausea and vomiting: exploring patients' subjective experience. J Multidiscip Healthc 2016;9:145-51.
5. Chinda M, Jaturapatporn D, Kirshen AJ, Udomsubpayakul U. Reliability and validity of a Thai version of the edmonton symptom assessment scale (ESAS-Thai). J Pain Symptom Manage 2011 ;42:954-60.
6. MASCC antiemesis tool (MAT).[2019 Dec 31]. Available

from https://www.mascc.org/assets/Guidelines-Tools / mat_english_questionnaire_2010_2. pdf
7. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care 1991;7:6-9.
8. Badihian S, Choi EK, Kim IR, Parnia A, Manouchehri N, Badihian N,et al. Attitudes Toward Cancer and Cancer Patients in an Urban Iranian Population. Oncologist 2017;22:944-50.
9. Pratt M, Stevens A, Thuku M, Butler C, Skidmore B, Wieland LS,et al. Benefits and harms of medical cannabis: a scoping review of systematic reviews. Syst Rev 2019;8:320.
10. Hsieh RK, Chan A, Kim HK, Yu S, Kim JG, Lee MA,et al. Baseline patient characteristics, incidence of CINV, and physician perception of CINV incidence following moderately and highly emetogenic chemotherapy in Asia Pacific countries. Support Care Cancer 2015;23:263-72.
11. Shankar A, Roy S, Malik A, Julka PK, Rath GK. Prevention of Chemotherapy-Induced Nausea and Vomiting in Cancer Patients. Asian Pac J Cancer Prev 2015;16:6207-13.
12. Teoh D, Smith TJ, Song M, Spirtos NM. Care After Chemotherapy: Peripheral Neuropathy, Cannabis for Symptom Control, and Mindfulness. Am Soc Clin Oncol Educ Book 2018;38:469-79.

DOI:10.31557/APJCC.2020.5.2.101

RESEARCH ARTICLE

Profile and Outcome of Triple Negative Breast Cancer at a Tertiary Care University Hospital in Nepal

Suman Khanal[1], Yogendra P. Singh[1], Gita Sayami[2], Akihiko Ozaki[3]

[1]Department of GI and General Surgery, Tribhuvan University Teaching Hospital, Kathmandu, Nepal. [2]Department of Pathology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal. [3]Department of Breast Surgery, Jyoban Hospital of Tokiwa Foundation, Fukushima, Japan.

Abstract

Background: TNBC (Triple negative breast cancer) subtype (ER-/PR-/HER2-) of breast cancers are known for aggressive tumor biology and poor survival prospects, with high early relapse rate. However, little is known about the prevalence and characteristics of TNBC breast cancer in Nepal. **Objectives:** To clarify the geographical distribution, clinical profile and outcome of TNBC patients when compared with non-TNBC patients managed in tertiary care university hospital in Nepal. **Materials and Methods:** This is a study on prospective observational analyses of TNBC and non-TNBC patients managed at Tribhuvan University Teaching Hospital, Kathmandu from October 2015-March 2018. We collected and analyzed data on clinical profile, pathological tumor features and outcome of the two patient groups. **Results:** A total of 108 breast cancer patients were included in our study, 38 (35.2%) of which were TNBCs. Mean age at diagnosis was 49±12 years. Majority of TNBCs (29%) were concentrated in Terai districts compared to non-TNBCs (18.6%). Among TNBCs, 15.2% had tumor size 5 cm or more while only 11.9% had such finding in non-TNBCs. Majority of TNBCs and non-TNBCs were of invasive ductal carcinoma of NST histology (76.3 vs 90%). TNBC tumors were significantly of grade 3 (P value=0.003). Perineural invasion was seen more (15.8%) in TNBCs compared to 8.96% in non-TNBCs. On average, 23.6% of total nodes retrieved from axilla were positive for tumor in TNBCs compared to 21% in non-TNBCs. Three patients developed metastases in TNBCs of which two were to brain while 5 had metastases in non-TNBC with none to brain. Higher percentage of patients died in TNBC group (13.2 vs 7.1%). **Conclusions:** TNBCs are quite common, higher grade tumors with brain metastasis without particular geographic distribution.

Keywords: Breast cancer- invasive ductal- triple negative

Asian Pac J Cancer Care, **5 (2)**, 101-105

Submission Date: 02/27/2020 Acceptance Date: 05/05/2020

Introduction

Breast cancer is the most frequent cancer among women affecting 1.5 million people worldwide with greatest number of cancer related deaths [1]. In 2015, it accounted for approximately 15% of all cancer deaths among women [1]. Triple-negative breast cancer (TNBC) is a molecular subtype of breast cancer in which the estrogen receptor and progesterone receptor are not expressed, and human epidermal growth factor receptor 2 is not amplified or overexpressed [2]. This subtype accounts for 10-24% of breast cancer and is known for worse prognosis with early relapse compared with other subtypes of breast cancer [3-5]. The epigenetic epithelial to mesenchymal transition in TNBC could explain its high propensity for metastasis [6-8]. Despite increased risk of metastasis and locoregional recurrence, these tumors have good response to chemotherapy and those with pathologic complete response do better [9-10]. TNBC still remains an orphan disease in terms of the available therapeutic options, as chemotherapy is the only standard of care [11].

In Nepal, breast cancer accounts for 7.9% of cancer cases [12]. Management of both TNBC and non-TNBCs is multidisciplinary [13]. Although there are studies evaluating TNBC prevalence, there are no studies comparing TNBC with non-TNBC in Nepal [14-15]. This study aims to compare these two groups of breast cancer in terms of age, ethnicity, geographic distribution, histology,

Corresponding Author:
Dr. Suman Khanal
Department of GI and General Surgery, Tribhuvan University Teaching Hospital, Kathmandu, Nepal.
Email: sumandoc@iom.edu.np

grade, recurrence, metastasis and mortality.

Materials and Methods

Study setting, participants, and variables

This study was done at a tertiary care Tribhuvan University Teaching Hospital (TUTH), located at central region of Nepal, Kathmandu. In our clinical practice, all the breast cancer patients undergo fine needle aspiration cytology (FNAC) in early breast cancer and core needle biopsy (CNB) in locally advanced cases. Patients with early breast cancer undergo surgery (breast conserving surgery (BCS), oncoplasty or modified radical mastectomy) followed by chemotherapy with or without radiotherapy and adjuvant hormonal therapy for hormone positive cases. Those with locally advanced cases receive neoadjuvant chemotherapy to downstage tumor followed by surgery and radiotherapy. Hormone positive cases receive hormonal therapy. Metastatic cases are treated palliatively.

We considered a total of 140 histopathologically confirmed non-metastatic cases of breast cancer patients managed in our hospital from October 2015-March 2018. We performed a follow-up of these patients until December 2018 in determining their outcomes. Using the medical records, we collected data on age, ethnicity, district, menopausal status, histology, tumor size, grade, lymphovascular invasion, perineural invasion, lymph node status, neoadjuvant chemotherapy, pathological stage, recurrence, metastasis and mortality.

Staging was done with chest x-ray, ultrasound of abdomen and pelvis for early disease with the addition of computed tomography (CT) and MRI for locally advanced cases. TNBC was defined as ER negative, PR negative and HER2 neu 0/1+ cancers. A tumor was classified negative when ER and PR expression was <1% in tumor cell nuclei. HER2 neu 2+ were considered equivocal/borderline [16] that needed FISH for confirmation but due to high costs and availability, were rarely done. HER2 neu 2+ cases were thus excluded from the study. Our treatment practices at two specialized cancer hospitals also show that targeted therapy against HER2 neu are rarely used due to forbidding high costs. For receptor status determination, it was done on Trucut biopsy sample in cases who received neoadjuvant therapy while it was done on specimen who received surgery first.

Data analysis

The categorical data was analyzed using chi-squared/ fisher's exact test where deemed appropriate. Unpaired t-test was applied for comparison for numerical data. R version 3.6.1 was used to analyze the data, plot the geographical mappings; P value < 0.05 was considered significant.

Ethical clearance

Ethical clearance was obtained from Institutional Review Board at the Tribhuvan University Teaching Hospital and consent was taken from all patients.

Results

Figure 1 shows the process in which we chose the patients for the study. After excluding cases with no receptor status data, HER2 neu equivocal cases and a case of squamous cell carcinoma, total of 108 cases were enrolled in the study.

Table 1 shows the patient characteristics. Out of 108 cases studied at our institute, 38 cases (35.2%) were TNBC. Mean age at diagnosis was 49±12 years in TNBC group as compared to 50±11 years in non-TNBCs (P value=0.88). Three patients in non-TNBC were males while TNBCs were all females. Eight of 38 (21.1%) TNBC and 13 of 70 (18.6%) non-TNBC patients were 40 years or younger (Table 1).

TNBC prevalence was 43.6% (24/55) in Indo-Aryans vs 26.4% (14/53) in Tibeto-Burman. Though it suggests higher percentage of TNBC among Indo-Aryans, it was not significantly different, and it could be expected, as their population share is 79% according to 2011 census of Nepal.

Geographically TNBC patients were concentrated more in southern districts of Nepal (29%) compared to non-TNBCs (18.6%) though it was not statistically significant (Figure 2 and Figure 3).

Among TNBCs, 57.9% and among non-TNBCs, 53.7% were premenopausal. Greater proportion of patients was of invasive ductal carcinoma, no special type in TNBCs (76.3%) against 90% in non-TNBC. It was however not statistically different (P value=0.10). The second most common histology in TNBC was invasive carcinoma with medullary features while it was ductal carcinoma in situ (DCIS) in non-TNBC (Table 2).

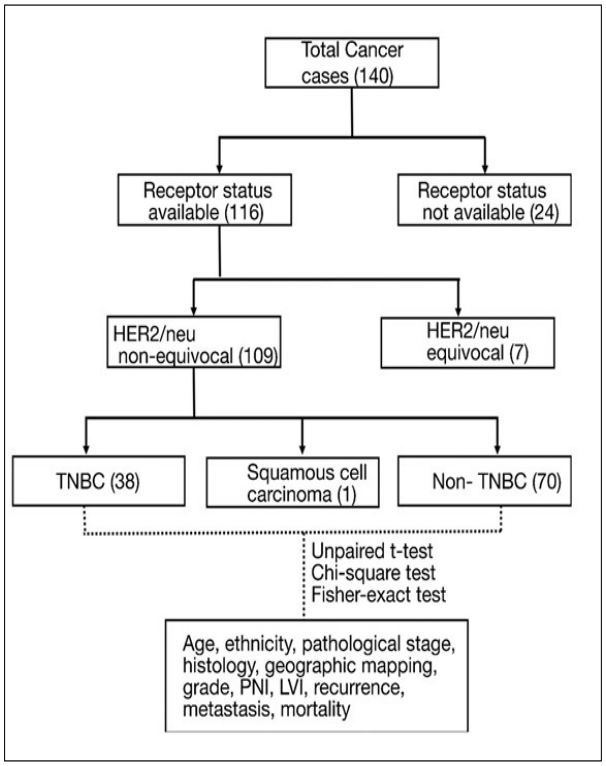


Figure 1. Patient Enrollment

Table 1. Comparison of Patient and Tumor Characteristics

	TNBC	Non-TNBC	P value
Mean age at diagnosis (years)	49±12	50±11	0.88
≤40 years	8 (21.1%)	13 (18.6%)	0.95
Tibeto-Burman	14 (36.8%)	39 (55.7%)	0.09
Terai districts	11 (29%)	13 (18.6%)	0.32
Premenopausal	22 (57.9%)	36 (53.7%)	0.46
Invasive ductal carcinoma, NST	29 (76.3%)	63 (90%)	0.10
Tumor size ≥5cm	5 (15.2%)	7 (11.9%)	0.90
Grade 3 histology	12 (31.6%)	5 (7.5%)	0.003
Lymphovascular invasion	18 (47.4%)	39 (58.2%)	0.39
Perineural invasion	6 (15.8%)	6 (8.96%)	0.46
Lymph node metastasis	17 (51.5%)	28 (47.5%)	0.88
Pathological stage 3	14 (42.4%)	20 (33.9%)	0.56
Locoregional recurrence	1 (2.6%)	4 (5.7%)	0.8
Metastasis	3 (7.9%)	5 (7.1%)	1
Mortality	5 (13.2%)	5 (7.1%)	0.5

Table 2. Distribution of Histological Types

TNBC		Non-TNBC	
Histological type	Number	Histological type	Number
Invasive CA NST	29	Invasive CA NST	63
Invasive CA with medullary features	4	DCIS	3
Invasive CA with mucinous component	2	Invasive lobular carcinoma	2
Metaplastic carcinoma	1	Invasive carcinoma with apocrine differentiation	1
Mixed invasive CA NST + Invasive lobular carcinoma	1	Solid papillary carcinoma	1
Mucinous carcinoma	1		

TNBCs had higher percentage (15.2%) of tumors with pathological tumor size 5 cm or more while 11.9% had such finding in non-TNBCs though it was not statistically significant (P value=0.90). The cases who received neoadjuvant therapy were not considered for pathological tumor size evaluation. Five and eleven patients had received neoadjuvant chemotherapy in TNBC and non-TNBC respectively.

Tumors were of higher grade (Grade 3) in 31.6% in TNBCs against only 7.5% in non-TNBCs, which was statistically significant (P value=0.003). Lymphovascular invasion (LVI) was seen in 47.4% of TNBCs compared to 58.2% in non-TNBCs (P value=0.39). Perineural invasion (PNI) was seen more (15.8%) in TNBCs compared to 8.96% in non-TNBCs. It was however not statistically significant (P value=0.46). For uniformity, three cases with DCIS in non-TNBC were excluded from tumor grade, lymphovascular invasion and perineural invasion analysis.

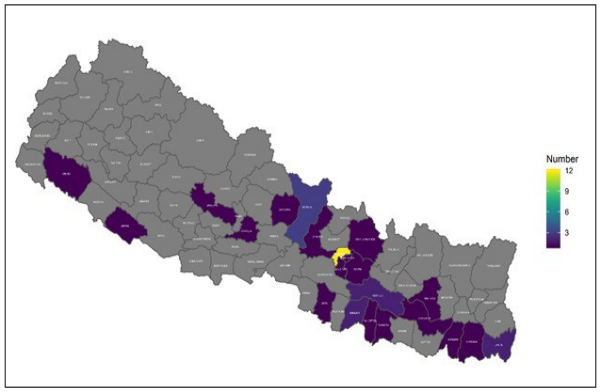


Figure 2. Geographic Distribution of TNBC Patients Across the Districts

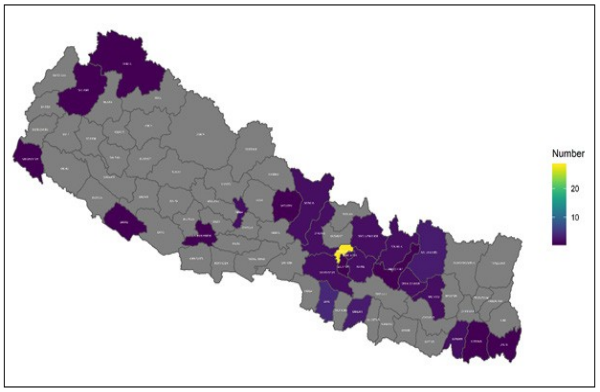


Figure 3. Geographic Distribution of Non-TNBC Patients Across the Districts

Excluding cases who received neoadjuvant chemotherapy, lymph node metastases were present in 51.5% cases in TNBC and 47.5% in non-TNBC. On average, 23.6% of total nodes retrieved from axilla were positive for tumor compared to 21% in non-TNBCs. Among TNBCs, 42.4% presented at pathological stage 3 while only 33.9% of non-TNBCs presented at this stage (P value=0.56).

One patient developed locoregional recurrence in TNBC (2.6%) against four in non-TNBC (5.7%). Three patients developed metastasis in TNBC (7.9%), one to abdomen and two to brain while none developed metastasis to brain in non-TNBC. In fact, among five (7.1%) who developed metastasis in non-TNBC, two were to bone and liver both, two to bone only and one to liver only. All metastases along with additional two cases died in TNBC (13.2%) while five cases succumbed in non-TNBC (7.1%).

Discussion

This study was done to evaluate the geographical distribution, demographic profile and tumor characteristics of TNBCs and compare them with non-TNBCs.

Our study identified 35.2% of breast cancer to be TNBC cases, which is consistent with previous literature suggesting higher cases of TNBC in South Asian countries (Nepal [17] and North India [18]) compared to 10-24% in the West [3-4]. However it was less than the incidence of 41.3% reported in another study in Nepal [15]. Both of our groups had lower number of patients 40 years or below but percent of total nodes positive for tumor was higher in this younger group (39.5% in TNBC and 33.2% in non-TNBC). Literature shows that breast cancer in young patients are often triple negative [14-19] but our study and a study in large cohort in Brazil does not support it [20]. TNBCs are noted to occur in younger blacks and Hispanics in the west [19-21]. In our setup, TNBC was more prevalent in Indo-Aryans, though the difference was not statistically significant. There was no literature evaluating this difference in Nepal.

Though statistically insignificant, geographic mapping of cancer cases showed TNBC to be more concentrated towards Terai districts. Terai districts are relatively hotter and as expected receive more sunlight due to their closeness to equator. One study from Turkey had found similar finding [22]. It would be very interesting to do a prospective study in a large cohort to test this hypothesis.

TNBCs are reported to be more common among pre-menopausal females [21-23-24]. However, this finding was not seen in our study, and neither the number of premenopausal females was high among TNBC.

Majority of TNBCs were invasive carcinomas of no special type similar to other studies [5-24-25]. Even the majority of non-TNBC were also invasive carcinomas of no special type similar to a study in Brazil [20].

Perineural invasion was seen more in TNBC group and lymphovascular invasion in non-TNBC, though it was not significantly different. Lymph node involvement was similar in two groups similar to a study in Brazil [20]. Many studies cite TNBC to be larger than non-TNBC [21-26]. However in our study, taking the cutoff of 5 cm, tumor size was not significantly different in two groups. In a study done in Brazil, even while taking a lower threshold of 2 cm, two groups were not significantly different at 95% significance [20]. TNBC tumors in our cohort was significantly of higher grade (Grade 3) which is consistent with other studies [19-21-24-27]. Also, TNBC had aggressive histological types like invasive carcinoma with medullary features and metaplastic carcinoma. Even in a multimodal annual screening done to detect cancer cases, grade 3 cancers were more in TNBC [28].

Many studies report the percentage of patients with positive axillary lymph nodes. We calculated average percentage of positive nodes out of total nodes retrieved from axilla. It was however not different between two groups. It would be interesting to evaluate this variable in large cohort. Number of recurrence and metastasis were similar in two groups similar to study in Brazil [20]. Interesting to note was two patients in TNBC cohort who had brain metastasis while none had in non-TNBC. This was as expected in the literature [21-26-29]. Mortality, though high in TNBC, was not statistically different in contrast to studies which report high mortality and early recurrence in TNBC [20-21-26]. This could be due to our small sample size and short follow up.

The main limitation was that the study center was a single center study which, might not represent all patients receiving treatment across Nepal.

In conclusion, TNBCs are quite common, higher grade tumors with brain metastasis without particular geographic distribution.

Acknowledgements

We would like to thank Research Department of Tribhuvan University Teaching Hospital which supported this work.

Funding statement

There was no source of funding for this research.

References

1. WHO | Breast cancer. (n.d.). WHO. Retrieved February 28, 2018, from http://www.who.int/cancer/prevention/diagnosis-screening/breast-cancer/en/ [
2. Marotti JD, de Abreu FB, Wells WA, Tsongalis GJ. Triple-Negative Breast Cancer: Next-Generation Sequencing for Target Identification. The American journal of pathology. 2017;187(10):2133-8.
3. Dawood S. Triple-negative breast cancer: epidemiology and management options. Drugs. 2010;70(17):2247-58.
4. Jitariu AA, Cimpean AM, Ribatti D, Raica M. Triple negative breast cancer: the kiss of death. Oncotarget. 2017;8(28):46652-62.
5. Schmadeka R, Harmon BE, Singh M. Triple-negative breast carcinoma: current and emerging concepts. American journal of clinical pathology. 2014;141(4):462-77.
6. Sikandar SS, Kuo AH, Kalisky T, Cai S, Zabala M, Hsieh RW, et al. Role of epithelial to mesenchymal transition

associated genes in mammary gland regeneration and breast tumorigenesis. Nature communications. 2017;8(1):1669.
7. Su Y, Hopfinger NR, Nguyen TD, Pogash TJ, Santucci-Pereira J, Russo J. Epigenetic reprogramming of epithelial mesenchymal transition in triple negative breast cancer cells with DNA methyltransferase and histone deacetylase inhibitors. Journal of experimental & clinical cancer research: CR. 2018;37(1):314.
8. Yang J, Mani SA, Donaher JL, Ramaswamy S, Itzykson RA, Come C, et al. Twist, a master regulator of morphogenesis, plays an essential role in tumor metastasis. Cell. 2004;117(7):927-39.
9. Carey LA, Dees EC, Sawyer L, Gatti L, Moore DT, Collichio F, et al. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clinical cancer research : an official journal of the American Association for Cancer Research. 2007;13(8):2329-34.
10. Liedtke C, Mazouni C, Hess KR, Andre F, Tordai A, Mejia JA, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(8):1275-81.
11. Park JH, Ahn JH, Kim SB. How shall we treat early triple-negative breast cancer (TNBC): from the current standard to upcoming immuno-molecular strategies. ESMO open. 2018;3(Suppl 1):e000357.
12. GLOBOCAN. IARC https://gco.iarc.fr/today/data/factsheets/populations/524-nepal-fact-sheets.pdf2018 [
13. Singh YP, Sayami P. Management of breast cancer in Nepal. JNMA; journal of the Nepal Medical Association. 2009;48(175):252-7.
14. Acharya SC, Jha AK, Manandhar T. Clinical profile of patients presenting with breast cancer in Nepal. Kathmandu University medical journal (KUMJ). 2012;10(39):3-7.
15. Nepal B, Singh, Y., Sayami, P., & Sayami, G. An institutional review of tumour biology of breast cancer in young Nepalese women. Journal of Society of Surgeons of Nepal. 2017;18(2):16-9.
16. Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(1):118-45.
17. Gupta M, Khanna, S., Kumar, M., Kar, A. G., & Gupta, S. K. Epidemiological Study of Triple-Negative Breast Cancer Patients in North Indian Population: A Hospital-Based Study. Indian Journal of Surgical Oncology 2017;8(3):279-83.
18. Shakya S. Epidemiology and clinical profile of breast cancer in central Nepal: A single institutional experience. Journal of Clinical Oncology. 2017;35((15_suppl)):e12008–e.
19. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer. 2007;109(9):1721-8.
20. Goncalves H, Jr., Guerra MR, Duarte Cintra JR, Fayer VA, Brum IV, Bustamante Teixeira MT. Survival Study of Triple-Negative and Non-Triple-Negative Breast Cancer in a Brazilian Cohort. Clinical Medicine Insights Oncology. 2018;12:1179554918790563.
21. Foulkes WD, Smith, I. E., & Reis-Filho, J. S. Triple-Negative Breast Cancer New England Journal of Medicine. 2010;363(20):1938–48.
22. Mutlu H, Buyukcelik A, Colak T, Ozdogan M, Erden A, Aslan T, et al. Is sunlight a predisposing factor for triple negative breast cancer in Turkey? Asian Pacific journal of cancer prevention : APJCP. 2013;14(2):801-3.
23. Boyle P. Triple-negative breast cancer: epidemiological considerations and recommendations. Annals of oncology: official journal of the European Society for Medical Oncology. 2012;23 Suppl 6:vi7-12.
24. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. Jama. 2006;295(21):2492-502.
25. Carey L, Winer E, Viale G, Cameron D, Gianni L. Triple-negative breast cancer: disease entity or title of convenience? Nature reviews Clinical oncology. 2010;7(12):683-92.
26. Elsawaf Z, Sinn HP. Triple-Negative Breast Cancer: Clinical and Histological Correlations. Breast care (Basel, Switzerland). 2011;6(4):273-8.
27. Kreike B, van Kouwenhove M, Horlings H, Weigelt B, Peterse H, Bartelink H, et al. Gene expression profiling and histopathological characterization of triple-negative/basal-like breast carcinomas. Breast cancer research : BCR. 2007;9(5):R65.
28. Podo F, Santoro F, Di Leo G, Manoukian S, de Giacomi C, Corcione S, et al. Triple-Negative versus Non-Triple-Negative Breast Cancers in High-Risk Women: Phenotype Features and Survival from the HIBCRIT-1 MRI-Including Screening Study. Clinical cancer research : an official journal of the American Association for Cancer Research. 2016;22(4):895-904.
29. Heitz F, Harter P, Lueck HJ, Fissler-Eckhoff A, Lorenz-Salehi F, Scheil-Bertram S, et al. Triple-negative and HER2-overexpressing breast cancers exhibit an elevated risk and an earlier occurrence of cerebral metastases. European journal of cancer (Oxford, England: 1990). 2009;45(16):2792-8.

DOI:10.31557/APJCC.2020.5.2.107

RESEARCH ARTICLE

Relative Frequencies and Patterns of Malignant Lymphoma in a Reference Centre in Khartoum, Sudan: A Descriptive Study Based on the WHO Classification of Lymphoid Neoplasms

Ezeldine K Abdalhabib

Department of Clinical Laboratory Sciences- College of Applied Medical Sciences-Qurayyat-Jouf University- Saudi Arabia.

Abstract

Background: The effective management and choice of appropriate treatment of lymphoma subtypes depend on an accurate diagnosis and differentiation, which require comprehensive haematology and pathology work. **Methods:** A total of 134 cases of malignant lymphoma, newly diagnosed between January 2017 to January 2020, were selected. For each patient's samples, complete blood count, immunohistochemistry, and morphological evaluation were done. **Results:** Clinical data showed that 81 patients (60.4%) were males and 53 (39.6%) females. The age range was 4 to 80 years. NHL lymphoma comprised 87.3% of cases, while HL comprised 12.7% of cases. Diffuse large B cell lymphoma was the most prevalent NHL subtype, representing 39.3% of cases. Among HL subtypes, mixed cellularity was present in 41.2% of cases. B cell lymphoma constituted 93.2% of cases. All HL patients and 74.4% of NHL patients had anaemia. **Conclusion:** This is the first statistical report of malignant lymphoma patterns in Sudanese patients. These data suggest that malignant lymphoma in Sudanese patients is more frequent in males than females; its incidence increases with age. Further, B cell lymphoma is more common than T cell lymphoma. Diffuse large B cell lymphoma was the most frequent NHL subtype.

Keywords: Malignant Lymphoma- Lymphoid Neoplasms- Sudan- frequencies- subtypes

Asian Pac J Cancer Care, **5 (2)**, 107-112

Submission Date: 04/24/2020 Acceptance Date: 06/15/2020

Introduction

Lymphomas comprise a heterogeneous group of clinically distinct neoplasms with varied aetiologies, outcomes, and treatment strategies [1-2]. The main types of lymphoma are non-Hodgkin lymphomas (NHL) and Hodgkin lymphomas (HL) ad defined by the lymphoid cells from which the neoplasm originates, which can be either B-cell, T-cell or NK-cell neoplasms. The World Health Organization (WHO) classifies lymphomas in more than 90 subtypes, including provisional types [3]. According to reports of the International Agency for Research on Cancer (IARC), the incidence rate of lymphoma is 3.5% of all cancers, with 589,580 new patients worldwide in 2018 and 274,891 deaths from the disease [4].

Although several reports exist regarding the distribution of malignant lymphomas in different parts of the world, no studies have been previously reported on the pattern of malignant lymphoma in Sudan. In Sudan, lymphoma represents the fourth most prevalent type of cancer in adults and the second in children's neoplasms [5]. The effective management and choice of appropriate treatment of lymphoma subtypes depend on an accurate diagnosis and differentiation, which require comprehensive haematology and pathology work. Immunohistochemistry is an essential diagnostic tool for distinguishing different lymphoma subtypes, besides histopathological evaluation of patient's samples. The presence of irregular margins in aggregated atypical lymphocytes is the main feature of malignant lymphoid cells [6]. However, indistinct cases are seen sometimes when biopsy samples are stained with routine stain only, i.e. haematoxylin and eosin (H&E), which has a significant impact on the treatment plan. Morphological evaluation, together with immunophenotyping and genetic studies,

Corresponding Author:
Dr. Ezeldine K Abdalhabib
Department of Clinical Laboratory Sciences- College of Applied Medical Sciences-Qurayyat-Jouf University- Saudi Arabia.
Email: ezeldine2008@yahoo.com

must be employed to achieve an accurate diagnosis for malignant lymphoma [7]. Immunohistochemistry is widely used for diagnosis and differentiation of malignant lymphoma [8]. The most commonly used biomarkers are CD3 and CD20 for T cell and B cell lymphoma, respectively [9]. The expression of biomarkers on lymphoid cells and subclasses of lymphoma are a dependent factor in the therapeutic intervention [10]. This study aims to investigate the relative frequency and pattern of different types of malignant lymphomas in Sudanese patients, according to the WHO classification of lymphoid neoplasms.

Materials and Methods

The current cross-sectional descriptive study was conducted at Radioisotope Centre of Khartoum (RICK), which is the reference oncology centre in Sudan. The study subjects included 134 newly diagnosed patients with different subtypes of HL or NHL of three years duration, diagnosed between January 2017 and January 2020. Ethical approval was obtained from the institutional ethical board. Patients already on treatment were excluded from the study. The determination of ML sub-types was based on WHO criteria. About 3 ml of venous blood were collected in EDTA-containing tubes after obtaining written informed consent from each patient or their parents for those aged under 18 years to participate in this study. Personal and clinical data including age, sex, and past medical history were collected using a questionnaire. In all cases, the blood sample was used for complete blood counts using a five-part automated analyser (Sysmex XP-300 ™, Kobe, Japan).

Morphological and immunohistochemical studies

From clinically suggestive lymphoma patients, consecutive excisional biopsies were obtained. The specimens related to lymph nodes (104 cases), abdominal tissues (13 cases), spleens (8 cases), soft tissues (5 cases), and head–neck tissues (4 cases). Using well fixed, processed, and embedded biopsy, multiple sections were selected and then stained with H&E, and wherever required, special staining was performed for the examination of histological pattern and infiltration. Three expert haematopathologists then reviewed all of the cases. Each expert independently reviewed all of the data available for each case. A consensus diagnosis was reached when two of the experts agreed on the diagnosis. H&E staining allowed sorting lymphomas between HL and NHL, according to the presence of different cells. Morphological diagnosis of HL cases was based on the effacement of nodal architecture by diffuse small lymphocyte cell, mononuclear, and multinucleated lymphocyte cell, prominent nucleus, a feature of Reed Sternberg cell, a feature of Hodgkin's cell, aggregated stroma with reactive histocytes and fibrosis. The included NHL features were effacement of sections by the mononuclear population of lymphocyte cells, dysplasia, increased N:C ratio, suppressing normopoeisis, and mixed cellular infiltration. DLCL presented with a diffused infiltrate of large noncleaved or transformed lymphocytes. Follicular lymphoma was characterised by effacement with mononuclear lymphocyte, and the centre of nodules were composed of pleomorphic lymphocyte with prominent nuclei as well as crowded, back-to-back neoplastic follicles, lack of zonation and tingible body macrophages, numerous cleaved cells, and loss of the mantle zones. BL sections presented with focal and effaced mononuclear cells, prominent nuclei and suppressing normal hemopoiesis. Malt lymphoma sections showed multiple fragments of gastric mucosa infiltrated by a mononuclear population of enterocyte-like lymphocyte destructive gastric gland (lymph epithelial lesion) adjusted showing intestinal metaplasia. T cell lymphoma presented with fragment mesenteric lymph node showing the suggestive feature of hyperplasia, no malignancy was observed in the section but extensive necrosis was found, visible cells showed a sheet of irregular lymphocytes with scattered macrophages.

Immunohistochemistry staining was prepared on specimens embedded with paraffin wax from the main tumours to confirm the morphological diagnosis by following the same techniques described in [11]. A panel of markers was selected based on morphologic diagnosis, including CD3, CD20, CD10, CD15, CD5, and CD30.

Statistical analysis

Data analysis was performed using Statistical Package for the Social Sciences (SPSS version 20.0) and Microsoft Office Excel 2010 for Windows. Qualitative and quantitative variables were described. The criterion for statistical significance was $P<0.05$.

Results

The 134 patients diagnosed with lymphoma were distributed into the traditional categories of non-Hodgkin and Hodgkin lymphoma and are included, along with sub-type and gender in Table 1. Seventeen (12.7%) cases were diagnosed as HL, whereas 46 (87.3%) were classified as NHL. Regarding HL, four subtypes were identified: mixed cellularity was the most prevalent subtype (41.2%), followed by nodular sclerosis and lymphocyte-rich (4 case; 23.5% for each), and lymphocyte-depleted lymphoma (11.8%). Of the NHL subtypes, DLBCL was the most prevalent type, representing 46 of the 117 cases (39.3%). BL was the second most common type, with 40 diagnosed cases (34.2%), followed by follicular lymphoma and small lymphocytic with a rate of 9 cases (7.7%) for each. Males were predominant in both types of lymphoma with overall 81 (60.4%) males and 53 (39.6%) females, a male: female ratio of 1.5:1. Among HL patients, 12 out of 17 patients (70.6%) were males, and (29.4%) females. In NHL patients, males and females were (69 cases; 59%, 48 cases; 41%, respectively).

Concerning age, as shown in Table 2, thirty nine (29.1%) were >60 years of age, and (70.9%) were <60 years of age. The youngest of these patients was four years old and the oldest 80 years old, with a mean age of 41 years.

Table 1. Frequency of Lymphoma and Lymphoma Subtypes within Studied Subjects Classified by Gender

Lymphoma Sub-types/Gender	Male	Female	Frequency
Hodgkin's lymphoma (HL)	12	5	17 (12.7%)
Nodular sclerosis	3	1	4 (23.5%)
Mixed cellularity type	5	2	7 (41.2%)
Lymphocyte rich	2	2	4 (23.5%)
Lymphocyte depleted	2	0	2 (11.8%)
Non-Hodgkin's lymphoma (NHL)	69	48	117 (87.3%)
Diffused large B Cell Lymphoma (DLBCL)	27	19	46 (39.3%)
Burkett's Lymphoma (BL)	25	15	40 (34.2%)
Small lymphocytic lymphoma	5	4	9 (7. 7%)
Extranodal marginal (MALT) lymphoma	3	1	4 (3.4%)
Follicular lymphoma	4	5	9 (7.7%)
T-cell-rich B cell lymphoma	1	0	1 (0.85%)
Peripheral T cell lymphoma	3	2	5 (4.3%)
Anaplastic Large Cell Lymphoma	0	1	1 (0.85%)
Precursor/lymphoblastic lymphoma	1	1	2 (1.7%)
Total	81	53	134

Table 2. Age Groups within Lymphomas Cases

Type of lymphoma/Age group		≤ 15 years	16-30 years	31-45 years	46-60 years	>60 years	Total
Hodgkin's lymphoma							
Mean ± SD	Range	3	3	2	4	5	17
47.14 ± 22.31 years	7-70 years						
Non- Hodgkin's lymphoma							
Mean ± SD	Range	33	10	18	22	34	117
40.22 ± 24.62 years	4- 80 years						
Total (%)		36 (26.90%)	13 (9.70%)	20 (14.90%)	26 (19.40%)	39 (29.10%)	134 (100%)
Overall mean of age =41.13±24.242 years/ Significance: χ^2 =0.69, P=0.952							

There was no statistically significant difference within age groups (P=0.952). As shown in Table 3, 109 (93.2%) of B cell lymphoma cases were identified compared to 8 (6.8%) cases belonging to T cell lymphoma. The expression of CD20 was identified in all B cell lymphomas and was not detected in any T cell lymphomas. CD3 was expressed in all T cell lymphomas and was also seen in one case of diffuse large B cell lymphoma. All HL cases expressed CD30 and CD15, with no expression of CD3, CD5, and CD10. CD20 was detected in the lymphocyte-rich subtype and one case of mixed cellularity type.

Haematological changes in patients with lymphoma are listed in Table 4. The prevalence of anaemia was evaluated by measuring the haemoglobin concentration. At enrolment, it was observed that all HL patients had anaemia with a mean haemoglobin level of 9.81 g/dl, ranging from 7.3 to 11.6 g/dl. Eighty-seven NHL patients (74.4%) had anaemia, with an average haemoglobin level of 10.7 g/dl. Leucocytosis of a variable degree was observed in 56 (47.9%) of NHL cases. The mean platelet count among patients with HL and NHL was 389.17 and 261.88 x 10^9 cell/L, respectively. Thrombocytosis was observed in seven cases (41.2%) of patients with HL. The mean leucocyte count was 18.65 and 17.02 x 10^9 cell/L in HL and NHL patients, respectively.

Discussion

This study confirms that diffuse large B cell lymphoma as an NHL subtype, and mixed cellularity in HL subtype are highly prevalent in Sudanese malignant lymphoma patients. The current study was conducted to provide data that may contribute to better health planning and understanding of potential predisposing factors for ML in Sudan, by investigation the relative distribution of various types of ML not previously investigated. In developing countries the prevalence and incidence rates of lymphoma as well as the distribution of lymphoma subtypes may vary (12-14). In the current study, HL and NHL were diagnosed in 12.7% and 87.3% of cases, respectively, which is consistent with the results of a survey conducted among ML patients in the United Kingdom, [15] Poland, [16] and also in ML patients in the United States [17] and Chinese ML patients [18]. However, among NHL subtypes in the present study, diffused large B cell lymphoma was the most prevalent subtype, which was identified in 39.3% of patients. Similar findings were reported in Sudan [19], as well as in India [20]. DLBCL has also

Table 3. Markers of Expression within Lymphomas Cases

Lymphoma Sub-types/Immuophenotype	CD 3	CD5	CD10	CD15	CD20	CD30
Hodgkin's lymphoma						
Nodular sclerosis	-	-	-	+	-	+
Mixed cellularity type	-	-	-	+	±	+
Lymphocyte rich	-	-	-	+	+	+
Lymphocyte depleted	-	-	-	+	-	+
Non- Hodgkin's lymphoma						
Diffused large B Cell Lymphoma (DLBCL)	± *	±	±	NA	+	NA
Burkett's Lymphoma (BL)	-	-	+	NA	+	NA
Small lymphocytic Lymphoma	-	+	-	NA	+	NA
Extranodal marginal (MALT) lymphoma	-	-	-	NA	+	NA
Follicular lymphoma	-	-	±	NA	+	NA
T-cell-rich B cell lymphoma	+	+	-	-	+	NA
Peripheral T cell Lymphoma	+	+	-	NA	-	NA
Anaplastic Large Cell Lymphoma	+	+	-	+	-	+
Precursor T lymphoblastic Lymphoma	+	+	+	-	-	NA

*One case of DLBCL gave positive reaction with CD3.

been documented to be the most frequent NHL subtype in most studies worldwide, and geographic variations in NHL subtypes are well documented. In Pakistan 66.1% of NHL cases were reported to be of DLBCL subtype [21]. In some African countries the distribution of NHL subtypes varies according to age group, with DLBCL accounting for 55% of all NHL cases among adults, [22] and BL comprising nearly 50% of childhood cases of NHL in Africa [23]. Regarding HL, mixed cellularity, was the more predominated type in the present study. Results were consistent with those found among Ethiopian ML patients [24]. In our study, the male gender group was more predominant in both types of lymphoma, with overall frequencies of 60.4% in males, and 39.6% in females. Among HL patients, 12 out of 17 patients were males. In NHL patients, males represented 59% of cases. These results are consistent with worldwide observations, which show that both ML and other haematological malignancies often occur more frequently in males than in females [17]. Concerning the characteristic patterns of lymphoma cells, B-cell lineage dominated in our current data (94%), compared to a low relative proportion of T cell lymphomas (6%). These findings are in agreement with previous studies [25]. However, the distribution of T cell lymphoma varies worldwide, ranging from a low frequency of about 4% such as in Korea [26], to more a frequent rate, such as 23% in Turkey [27]. In the present study, in ML cases expression of CD3 and CD20 were the most specific surface antigens for lymphocytes. CD20 was expressed in all B cell lymphomas and was negative in all T cell lymphomas while CD3 was expressed in all T cell lymphomas, and in one case of large B cell lymphoma. These results are consistent with previous studies in ML cases. Regarding the finding of one large B cell

Table 4. Variables of Peripheral Blood Parameters within Lymphomas cases

Haematological variables/ Type of Lymphoma	Hodgkin's lymphoma	Non- Hodgkin's lymphoma	P-value
Haemoglobin (Mean ±SD) g/dl	9.81 ±1.72	10.7 ± 2.17	0.312
Range of haemoglobin g/dl	7.30 - 11.60	6.00 - 15.20	--
Normal haemoglobin level N (%)	0 (0.00 %)	30 (25.6%)	0.084
Low haemoglobin level N (%)	17 (100%)	87 (74.4%)	0.082
Leucocyte count (Mean ±SD) cell/L	18.65±34.23	17.02±41.81	0.098
Range of leucocyte count, cell/L	2.30 -96.00	1.00 - 272.00	--
Normal leucocyte count N (%)	12 (70.6%)	49 (41.9%)	0.332
Leucocytosis N (%)	3 (17.6%)	56 (47.9%)	0.028
Leucocytopenia N (%)	2 (11.8%)	12 (10.3%)	0.849
Platelets count, cell/L (Mean ±SD)	389.17±239.46	261.88±161.45	0.097
Range of platelets count, cell/L	41.00 -762.00	15.00-636.00	--
Normal platelets count N (%)	5 (29.4%)	71 (60.7%)	0.021
Thrombocytosis N (%)	7 (41.2%)	18 (15.4%)	0.015
Thrombocytopaenia N (%)	5 (29.4%)	28(23.9%)	0.624

lymphoma case that gave a positive reaction for CD3, the same result has been reported in rare instances of mature B-cell neoplasms in some studies [28-30]. The explanation behind this odd finding remains unclear. However, several mechanisms have been suggested to clarify the aberrant expression of T-cell antigens by neoplastic B cells [31, 32]. Concerning the age of our study subjects, 29.1% were >60 years of age, and 70.9% were <60 years of age. The youngest of these patients was four years old and the oldest 80 years old, with a mean age of 41 years. These results were consistent with Caminha et al. study [33]. Evaluations of peripheral blood parameters are required as part of pre-treatment check-up in cases of lymphoma, parameters which are also reflective of prognostic inferences, especially if an abnormality is found [34]. In the current study, anaemia was the most frequent feature, found in all HL patients and the majority of NHL patients (74.4%). Leucocytosis was observed in 47.9% of NHL cases. Thrombocytosis was detected in 41.2%and 15.4% of patients with HL and NHL, respectively. Further, the frequency of leucopenia was observed in 11.8%, and 10.3% of patients with HL and NHL, respectively. These haematological variables did not show any statistically significant differences within studied lymphoma patients. These abnormalities, also observed in previous studies, may be initiated by the influence of cytokines released by malignant cells, and also as a consequence of bone marrow replacement by ML cells at the late stage of the disease [35-36]. ML in Sudanese patients was more frequent in males than in females; its incidence increases with age. B cell lymphoma is more common than T cell lymphoma. DLBCL was the most frequent NHL subtype.

Acknowledgments

I thank the staff of the Radioisotope Centre of Khartoum (RICK), especially the haematopathologists and clinicians, for their great help in sample collection and diagnosis. I would also like to thank all the participants who took part in this study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

None

References

1. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood. 2011 05 12;117(19):5019-5032. https://doi.org/10.1182/blood-2011-01-293050
2. Küppers R. The biology of Hodgkin's lymphoma. Nature Reviews Cancer. 2008 Dec 11;9(1):15-27. https://doi.org/10.1038/nrc2542
3. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016 05 19;127(20):2375-2390. https://doi.org/10.1182/blood-2016-01-643569
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018 09 12;68(6):394-424. https://doi.org/10.3322/caac.21492
5. Saeed M, Cao J, Fadul B, et al. A Five-year Survey of Cancer Prevalence in Sudan. Anticancer Res. 2016;36:279-86.
6. Schmid C, Isaacson PG. Bone marrow trephine biopsy in lymphoproliferative disease.. Journal of Clinical Pathology. 1992 09 01;45(9):745-750. https://doi.org/10.1136/jcp.45.9.745
7. Venizelos ID, I, Tatsiou ZA, Z, Mandala E E. Primary cutaneous T-cell-rich B-cell lymphoma: a case report and literature review. Acta Dermatovenerol Alp Panonica Adriat. 2008;17:177-81.
8. Rao I. Role of immunohistochemistry in lymphoma. Indian Journal of Medical and Paediatric Oncology. 2010;31(4):145. https://doi.org/10.4103/0971-5851.76201
9. Xiao W, Wang Z, Wang L. CD20-positive T-cell Lymphoma with Indolent Clinical Behaviour. Journal of International Medical Research. 2010 06;38(3):1170-1174. https://doi.org/10.1177/147323001003800347
10. Armitage JO. Early-Stage Hodgkin's Lymphoma. New England Journal of Medicine. 2010 08 12;363(7):653-662. https://doi.org/10.1056/nejmra1003733
11. Roudi R, Korourian A, Shariftabrizi A, Madjd Z. Differential Expression of Cancer Stem Cell Markers ALDH1 and CD133 in Various Lung Cancer Subtypes. Cancer Investigation. 2015 06 05;33(7):294-302. https://doi.org/10.3109/07357907.2015.1034869
12. Mohd Noor A, Sarker D, Vizor S, McLennan B, Hunter S, Suder A, Moller H, Spicer JF, Papa S. Effect of Patient Socioeconomic Status on Access to Early-Phase Cancer Trials. Journal of Clinical Oncology. 2013 01 10;31(2):224-230. https://doi.org/10.1200/jco.2012.45.0999
13. Perry AM, Diebold J, Nathwani BN, MacLennan KA, Müller-Hermelink HK, Bast M, Boilesen E, Armitage JO, Weisenburger DD. Relative frequency of non-Hodgkin lymphoma subtypes in selected centres in North Africa, the middle east and India: a review of 971 cases. British Journal of Haematology. 2015 Dec 18;172(5):699-708. https://doi.org/10.1111/bjh.13876
14. Perry AM, Perner Y, Diebold J, Nathwani BN, MacLennan KA, Müller-Hermelink HK, Bast M, Boilesen E, Armitage JO, Weisenburger DD. Non-Hodgkin lymphoma in Southern Africa: review of 487 cases from The International Non-Hodgkin Lymphoma Classification Project. British Journal of Haematology. 2015 Dec 21;172(5):716-723. https://doi.org/10.1111/bjh.13885
15. Smith A, Crouch S, Lax S, Li J, Painter D, Howell D, Patmore R, Jack A, Roman E. Lymphoma incidence, survival and prevalence 2004–2014: sub-type analyses from the UK's Haematological Malignancy Research Network. British Journal of Cancer. 2015 03 24;112(9):1575-1584. https://doi.org/10.1038/bjc.2015.94
16. Szumera-Ciećkiewicz A, Gałązka K, Szpor J, et al. Distribution of lymphomas in Poland according to World Health Organization classification: analysis of 11718 cases from National Histopathological Lymphoma Register project - the Polish Lymphoma Research Group study. Int J Clin Exp Pathol.7:3280-6.
17. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger

DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood. 2006 01 01;107(1):265-276. https://doi.org/10.1182/blood-2005-06-2508
18. Sun J, Yang Q, Lu Z, He M, Gao L, Zhu M, Sun L, Wei L, Li M, Liu C, Zheng J, Liu W, Li G, Chen J. Distribution of Lymphoid Neoplasms in China. American Journal of Clinical Pathology. 2012 09;138(3):429-434. https://doi.org/10.1309/ajcp7yltqpusdq5c
19. Ismail A, Osman I, Husain NE. LMP1 Immunohistochemistry in Non-Hodgkin's Lymphoma of Sudanese Cases. Open Journal of Pathology. 2016;06(02):79-87. https://doi.org/10.4236/ojpathology.2016.62010
20. Nair R, Arora N, Mallath MK. Epidemiology of Non-Hodgkin's Lymphoma in India. Oncology. 2016;91(1):18-25. https://doi.org/10.1159/000447577
21. Mushtaq S, Akhtar N, Jamal S, et al. Malignant lymphomas in Pakistan according to the WHO classification of lymphoid neoplasms. Asian Pac J Cancer Prev. 2008;9:229-32.
22. Naresh KN, Raphael M, Ayers L, Hurwitz N, Calbi V, Rogena E, Sayed S, Sherman O, Ibrahim HA, Lazzi S, Mourmouras V, Rince P, Githanga J, Byakika B, Moshi E, Durosinmi M, Olasode BJ, Oluwasola OA, Akang EE, Akenòva Y, Adde M, Magrath I, Leoncini L. Lymphomas in sub-Saharan Africa - what can we learn and how can we help in improving diagnosis, managing patients and fostering translational research?. British Journal of Haematology. 2011 06 28;154(6):696-703. https://doi.org/10.1111/j.1365-2141.2011.08772.x
23. Hämmerl L, Colombet M, Rochford R, Ogwang DM, Parkin DM. The burden of Burkitt lymphoma in Africa. Infectious Agents and Cancer. 2019 08 01;14(1). https://doi.org/10.1186/s13027-019-0236-7
24. Getachew A. Malignant lymphoma in western Ethiopia. East Afr Med J.78:402-4.
25. Hamid KH, Yousif BM, Abdel MM, Elduma AH. Immunophenotyping of Non-Hodgkin's lymphomas in Sudan. Pan African Medical Journal. 2014;18. https://doi.org/10.11604/pamj.2014.18.82.3732
26. Yoon SO, Suh C, Lee DH, Chi H, Park CJ, Jang S, Shin H, Park B, Huh J. Distribution of lymphoid neoplasms in the Republic of Korea: Analysis of 5318 cases according to the World Health Organization classification. American Journal of Hematology. 2010 08 30;85(10):760-764. https://doi.org/10.1002/ajh.21824
27. Sağlam A, Esin E, Hayran M, Boyraz B, Üner A. Distribution of lymphomas in Turkey: data of 4239 cases from a single institution using the WHO classification. Turk J Med Sci. 2018;48:1013-23. https://doi.org/10.3906/sag-1804-107
28. Wu B, Vallangeon B, Galeotti J, Sebastian S, Rehder C, Wang E. Epstein-Barr virus-negative diffuse large B cell lymphoma with aberrant expression of CD3 and other T cell-associated antigens: report of three cases with a review of the literature. Annals of Hematology. 2016 07 19;95(10):1671-1683. https://doi.org/10.1007/s00277-016-2749-0
29. Wang J, Chen C, Lau S, Raghavan RI, Rowsell EH, Said J, Weiss LM, Huang Q. CD3-positive Large B-cell Lymphoma. The American Journal of Surgical Pathology. 2009 04;33(4):505-512. https://doi.org/10.1097/pas.0b013e318185d231
30. Oliveira JL, Grogg KL, Macon WR, Dogan A, Feldman AL. Clinicopathologic Features of B-Cell Lineage Neoplasms With Aberrant Expression of CD3. The American Journal of Surgical Pathology. 2012 09;36(9):1364-1370. https://doi.org/10.1097/pas.0b013e31825e63a9
31. Lee M, Cha HJ, Yoon DH, Suh C, Huh J. EBV-positive diffuse large B-cell lymphoma of the elderly with aberrant expression of CD3 and TIA-1. Blood Research. 2013;48(2):156. https://doi.org/10.5045/br.2013.48.2.156
32. Yang L, Ingersoll K, Zhao Y, Luedke C, Sebastian S, Wang E. CD3-positive diffuse large B-cell lymphoma relapses as CD3-negative large B-cell lymphoma: Loss of aberrant antigen expression in B-cell lymphoma after chemotherapy. Pathology - Research and Practice. 2018 Oct;214(10):1738-1744. https://doi.org/10.1016/j.prp.2018.07.003
33. Caminha B, Neves Rodrigues Vieira G, Bragante Fernandes Pimenta M, et al. Epidemiological Analysis of Lymphoma Subtypes in a Reference Center in João Pessoa, Paraiba, Brazil. Int J Phys Med Rehabil. 2018;6:473.
34. Zhang Q, Foucar K. Bone Marrow Involvement by Hodgkin and Non-Hodgkin Lymphomas. Hematology/Oncology Clinics of North America. 2009 08;23(4):873-902. https://doi.org/10.1016/j.hoc.2009.04.014
35. Durosinmi M, Mabayoje V, Akinola N. A review of histology of bone marrow trephine in malignant lymphomas. Nigerian journal of medicine : journal of the National Association of Resident Doctors of Nigeria. 2003;12(4):198-201.
36. Mustafa A, Fatima Bhopalwala A. Incidence of Hodgkin's & Non Hodgkin's Lymphomas and Comparison of Their Hematological Parameters. JMSCR. 2018;6:218-21.

DOI:10.31557/APJCC.2020.5.2.113

RESEARCH ARTICLE

Awareness about Gynecological Cancers amongst Tribal Females

Neha Jha[1], Anita H Panot[2], Upendra Singh[3]

[1]Department of Psychiatry, Centre of Excellence in mental Health, ABVIMS & Dr. RML Hospital, New Delhi, India. [2]Assistant Professor, Department of Social Work, Nirmala Niketan, Mumbai University, Mumbai, India. [3]Faculty, Department of Psychiatry, Centre of Excellence in mental Health, ABVIMS & Dr. RML Hospital, New Delhi, India.

Abstract

Background: Gender differences are engrained in our culture and are evident when perceiving women's health and ill health. Health issues of women are of great importance in a society as it directly impacts the fabric of family and society. With limited access to education or employment, high illiteracy rates and increasing poverty levels health improvements for women are quite difficult in developing countries including India. There is a significant lack of official data on gynecological cancers further for women from tribal population which is important for advocacy and public health care planning. **Aim:** Study aimed at assessing awareness of gynecological cancers amongst tribal females in Borivali Taluka of Mumbai, Maharashtra. **Methodology:** The research is a descriptive study with a cross-sectional research design. 100 tribal female comprised the total sample. **Result:** Significant lack of awareness about the Gynecological cancers was seen in the tribal respondents of Aarey circle of Borivalli Taluka, Mumbai regarding the symptoms, treatment, and preventive measures of gynecological cancers. **Conclusion:** It is evident from previous as well as current study several factors are responsible for poor awareness about gynecological cancers among marginalized tribal respondents.

Keywords: Tribal health- gynecological cancers- health advocacy

Asian Pac J Cancer Care, **5 (2)**, 113-118

Submission Date: 04/28/2020 Acceptance Date: 06/17/2020

Introduction

Healthy living is important for healthy functioning, number of individuals living with health issues due to unawareness. Understanding of health issues can help treatment on time and proper care. There is a significant ignorance among women regarding the gynecological cancers because most of its symptoms are taken less seriously by the women as well as their families because of the traditional beliefs regarding the gynecological issues like vaginal bleeding and pain. The ignorance is somewhat same among the various groups irrespective of their socio-economic background because the way women's gynecological health is perceived in the family irrespective of it being the second biggest cause of mortality among women across the world [1].

Gynecological cancer is any cancer that occurs in a woman's reproductive organs. The gynecological cancers begin in different places within a woman's pelvis. Each cancer of female reproductive organ is unique, with different signs and symptoms, different risk factors targeted through different prevention strategies [2]. Women as a demographic are at the risk for gynecological cancers, and it has been established that the risk increases with age. Most gynecological cancers preventive by nature, if detected early have good prognosis.

As per GLOBOCAN, main types of cancer that account for most burden and affect a woman's reproductive organs are cervical, ovarian, uterine, vaginal, and vulvar [1].

WHO's comprehensive global cancer statistics of International Agency for Research on Cancer (IARC) states that almost 70 percent of the global burden falls in areas with lower development and also found that in India diagnosed more than one fifth of all new cases [3].

India's National Cancer Control Program has raised the significance of early detection and treatment. However, it has also been asserted there is no comprehensive screening program and the majority of Indian women have poor or

Corresponding Author:
Dr. Neha Jha
Department of Psychiatry, Centre of Excellence in mental Health, ABVIMS & Dr. RML Hospital, New Delhi, India.
Email: neha22.jha@gmail.com

no awareness about the disease. The access to prevention and treatment facilities are further adding to the treatment gap. Even though cancer screening programs have been made available in all the regional cancer centres and comprehensive cancer care specialty hospitals, it is restricted to only certain population coverage due to limited awareness and resources [4].

The epidemiological studies have pointed out at early age of marriage, multiple sexual partners, multiple pregnancies, poor genital hygiene, malnutrition, use of oral contraceptives, and poor awareness as risk factors. [5]. The first step towards controlling the cancer burden in target population is to know its status in the population and collect information about the relative access to healthcare facilities.

There is no previous study done on the tribal population residing in the city of Mumbai as reaching tribal population due them residing traditionally in the forest part of the city. This is is the pilot study done to assess the awareness about gynecological cancers amongst the tribal females in an urban city order to use the same for the public health advocacy of their major health issues.

Aim

The study aimed at assessing awareness of gynecological cancers amongst tribal females.

Materials and Methods

Ethical permission was collected from the department of Social Work, Mumbai University. Further permissions was taken from the tribal leaders to conduct the study in respective tribal hamlets and each participant was asked for their consent before any information was collected from them.

The study was a descriptive research. Cross-sectional research design was used and quantitative information was collected from the respondents. A total of 100 tribal female respondents were selected through purposive sampling technique from Borivali, Taluka of Mumbai, Maharashtra. Married females belonging to age group 20-55 years, belonging to a regional tribe, having no physical or psychiatric illness, after giving written consent for the present study were included in the study. Divorced, separated and widowed females were excluded from the study.

Tools

Socio-demographic Data Sheet

It was used to collect personal and clinical information of the respondents like – age, education, duration of marriage, substance use, history of physical illness, no. of hospitalization and nature of work etc.

Self prepared interview schedule

A self prepared interview schedule that was made with the expert from the field had 59 items. It was prepared in English than translated to Marathi language, after that reverse translation done with 6 (six) research expert working in same field, most appropriate questionnaire in Marathi language which can be easily comprehended by the respondents was used for data collection.

Procedure

At the very beginning ethical permission was taken from the Research and Ethics board of Department of Social Work, Mumbai University. Permission was further taken from the tribal leaders of respective tribal hamlets to conduct the study in their hamlet. Respondents were selected using purposive sampling technique considering inclusion and exclusion. Each participant was explained about the aim and procedure of the study in detail; following which consent were collected from them. Self prepared interview schedule was administered at the very end to collect data. The self prepared interview schedule was administered individually.

Results

Table 1 describes the distribution of socio-demographic variables of the respondents. Mean age was 32.53 and SD 10.03. Respondents were divided into three age groups, 38% respondents covered 20-30 years, 32% were 41-55 years and 30% respondents were 31-40 years age group. Majority of the respondents 42% educated up to higher secondary, comparison to 34% respondents were completed secondary education, 16% respondents educated up to primary and 8% were graduate. Respondents nature of work 36% were homemaker compare to 24% were engaged as Vendor, 16% worked as cook, only 10% respondents engaged skilled work, labor, fishing and students were 6%, 4% and 4% respectively.

Table 2 describes the respondents belong various sub division of the tribal community. Total participants comprised 9 tribal communities only one community respondents 20% due to further sub vision as compared to all other communities were represented 10% each.

Table 3 shows that related health services availability in participant's community, aganwadi service covered whole area and other only 46% respondents taken benefits of Pada services. Respondents understanding about cancer very significant they were not much aware about that sever illness like Vaginal Cancer 94% respondents are not aware in the same way Cervical, Ovarian, Brest and Uterine cancer also 80%, 74%, 64% and 62% respectively not aware.

Table 4 shows that sign and symptoms of cervical cancer among the respondents. Only 54% respondents were aware about irregular vaginal bleeding, 46% respondents know that vaginal discharge with unpleasant odor, similarly 22% were known that pelvic or back pain. Majority of the respondents 96%, 94% and 93% were not aware about problem defecating, swelling of legs, urinating and pain during intercourse also sign and symptoms of cervical cancer

Table 5 shows that awareness of sign and symptoms of ovarian cancer among the respondents. Only 27% and 26% respondents were aware about menstrual changes and abdominal swelling with weight loss respectively one

Table 1. Shows Distribution of Socio-demographic Variables among the Respondents

Variable	Mean (N=100)	Std. Dev.
Age	32.52	10.03
Age Group	Frequency (N=100)	Percentage
20-30	19	38
31-40	15	30
41-55	16	32
Education		
Primary	16	16
Secondary	34	34
Higher Secondary	42	42
Graduate	8	8
Nature of Work		
Labour	6	6
Cook / Maid	16	16
Vendor	24	24
Fishing	4	4
Skilled Worker	10	10
Homemaker	36	36
Student	4	4

third 73% and 74% were not aware. Similarly maximum respondents 96% were not aware like frequent bloating and trouble eating also basic sign of ovarian cancer.

Table 6 shows signs and symptoms of gynecological cancers experienced by the respondents. Astounding results reflected that pelvic and Back pain were experienced by 42% of the respondents while irregular vaginal bleeding was experienced by 36% of respondents and 38% reported having changes in menstrual pattern.

A staggering 88% who experienced these symptoms said that they didn't visit doctors for these symptoms. Reasons cited for the same were that 26% of respondents considered these symptoms not having a serious health risk, lack of time was also mentioned by 2% of respondents and 4% considered this as a normal issue. Symptoms getting cured on its own was belief of 6% of respondents for not visiting the doctor.

Discussion

The study was conducted in Aarey area of Borivali taluka of Mumbai region. For the study researcher chose 100 married respondents belonging to 10 Different tribes between the age group 20-55 who residing in different hamlets. Respondents mean Age was 32.52 and 10.03 SD, which divided in three groups. Analyzing the educational qualification of respondents, 8% were graduate it found that only young age group studying on to higher level. 42% respondents have studied till higher secondary after that they are engaged in personal work similarly 34% secondary and 16% of respondents were educated up to primary level. Research found that most of the respondents which is 36% were working as homemaker, they primarily worked at home and looked after children and weren't educated while 24% respondents were working as vendors with their family members. 16% of respondents worked as cooks or domestic helps for their living while 10% respondents were skilled worker, 6% labor work, 4% were fishing and studying. Notably except fishing, none of the

Table 2. Description of Tribe Community

Type of Tribe		
Audh	10	10
Dhoriya	10	10
Dubla	10	10
Katkari	10	10
Kokana	10	10
Koli Mahadev	20	20
Naykada	10	10
Thakkar	10	10
Warli	10	10

Table 3. Responses on Self Prepared Interview Schedule Services and Understanding

S. No.	Statements	Yes (%)	No (%)
1	Angarwadi Services (Community Health services)	100	0
2	Availability of tribal hamlet Services	46	54
3	Heard of Cervical Cancer	20	80
4	Heard of Ovarian Cancer	26	74
5	Heard of Uterine Cancer	38	62
6	Heard of Vaginal Cancer	6	94
7	Heard of Breast Cancer	36	64

Table 4. Awareness about Signs and Symptoms of Cervical Cancer

S. No.	Signs and Symptoms	Yes (%)	No (%)
1	Irregular vaginal bleeding	54	46
2	Vaginal Discharge with unpleasant odor	46	54
3	Pelvic or Back pain	22	78
4	Pain during intercourse	7	93
5	Problems urinating	6	94
6	Problem Defecating	4	96
7	Swelling of the legs	4	96

Table 5. Awareness about Signs and Symptoms of Ovarian Cancer

S. No.	Signs and Symptoms	Yes (%)	No (%)
1	Menstrual Changes	27	73
2	Frequent bloating	4	96
3	Trouble eating or upset stomach	4	96
4	Abdominal swelling with weight loss	26	74

tribal women were doing traditional tribal work to sustain a living as it would be difficult sustaining in the city of Mumbai without having work that was considerably paid.

The study suggested that apart from health, education of tribal respondents is neglected. A majority of respondents were young and in the age group between 20-30 years therefore the results of this study are especially significant since the actions taken based on this report will directly affect these respondents when it came to the preventive nature of the Gynecological cancers while the older aged respondents might not be able to benefit from the changes undertaken but can still be educated about the treatment aspect of the disease.

Anganvadi services (Community health services) covered whole area of study but Pada (hamlet) services pertaining to the specific issues of the tribe were not present at grassroot level as it was found that approximately half area, 46% covered Pada services. Result reflected that respondents that had heard about types of Gynecological cancer, Uterine cancers were known to 38% as compared to more fatal breast cancer which was 36% while Vaginal cancer was known only 6% of respondents. Out of 100

Table 6. Experiencing Signs and Symptoms of Gynecological Cancers

S. No.	Signs and Symptoms	Yes (%)	No (%)
1	Irregular vaginal bleeding	36	64
2	Vaginal Discharge with unpleasant odor	10	90
3	Pelvic or Back pain	42	58
4	Pain during intercourse	14	86
5	Problems during urinating	38	62
6	Problem Defecating	3	97
7	Swelling of the legs	12	88
8	Menstrual Changes	38	62
9	Frequent bloating / trouble eating/ upset stomach	18	82
10	Abdominal swelling with weight loss	24	76
11	Did you visit doctor with any of these symptoms?	12	88

only 20% of respondents had understanding about cervical cancer whereas this figure shows that 26% had heard of Ovarian cancer. Early detection of Gynecological cancer is possible if consideration is given to sign and symptoms pertaining especially to cervical cancer [6].

Lack of awareness among respondents which accounts for 80 % who had no knowledge regarding cervical cancer shows an alarming situation and needs to be addressed as it clearly reflects the gap between testing and diagnosis. Cervical cancer is the most common cause of cancer related deaths in developing countries [7]. In India deaths related to cervical cancer is 67,477 out of 122,844 who are diagnosed with this cancer. Most common age developing cancer in respondent's age between 15-44 years, India has high risk of 15 years and above among 432.2 million populations [8].

There is need of addressing the same on policy level that requires advocacy from NGO's and health activists to take this into account to spread awareness among marginalized groups.

Sign and symptoms of cervical cancer among the respondents were found that very severe condition. 54% respondents were aware about irregular vaginal bleeding, 46% respondents know that vaginal discharge with unpleasant odor, similarly 22% were known that pelvic or back pain. Majority of the respondents 96%, 94% and 93% were not aware about problem defecating, swelling of legs, urinating and pain during intercourse also sign and symptoms of cervical cancer as focused by Sreedevi et al [9].

Gynecological cancer in India presents a situation that needs to be controlled at the earliest. As reported by the GLOBOCAN 2018, China and India together contributed more than a third of the global cervical burden, with India reporting 97000 cases, and 60000 deaths [1].

Study finding that Ovarian Cancer also have less awareness among the respondents. Researcher has recorded lack of awareness among the respondents about the different forms of gynecological cancers. The most common of gynecological cancer among Indian women which is cervical cancer remains significantly unknown among the respondents. A striking factor study had founded the absence of knowledge among young respondents. When it has been reported by that there is high prevalence of HPV (Human Papilloma Virus) among tribal girls and young women in India which is the biggest risk factor for Cervical cancer [10].

When the researcher studied for awareness of symptoms and asked whether they posed any threat to their health most of the respondents have shown lack of awareness to the disease which these symptoms could lead to. Only irregular vaginal bleeding was considered a threat to health whereas all other symptoms were believed to be normal and something that can heal easily on its own. This clearly reflects the attitude of women towards their reproductive health by taking the symptoms like abdominal cramps and menstrual changes leniently that could be sign of diseases like gynecological cancers.

From the above table shows that abdominal and Back pain were experienced by 42% of the respondents. Irregular vaginal bleeding was experienced by 36% of respondents and 44% came across to changes in menstrual pattern. Total 26% of respondents considered these symptoms as non-serious and lack of time was also mentioned by 2% of respondents and 4% considered this as a normal issue. "Getting cured" on its own was said by 6% of respondents for not visiting the doctor. Study found that response to the symptoms that the respondents have faced or they were facing, reflected that due to unawareness they were not taking proper treatment which is the reason for poor prognosis. Mainly pelvic and abdominal pain were present in more than 70% respondents, this could be attributed to other factors not necessary considered as symptoms of cancer in them. Several factors which were holding back the respondents in getting treatment or visit the nearby clinic was in the same line as shown by the study of respondents belonging to lower socio-economic strata and lives in urban area.

In conclusion, lack of awareness was seen in the tribal respondents of Aarey circle of Borivalli Taluka, Mumbai regarding the symptoms, treatment, and preventive measures of gynecological cancers. As it is evident from previous as well as current study multiple factors are responsible for this unawareness among tribal respondents with literacy levels and effective infrastructure in government hospitals being a few of them. Most importantly, aches and menstrual changes are not seen as a symptoms or signs of a disease and hence is followed by negligence that is one of the main reasons affecting the preventive nature of gynecological cancers. Education can be one of the important tools of change in bridging this gap that will help tribal women to achieve better reproductive health. Awareness of tribal respondents belonging to older age group outside the purview of this study need to be studied that researcher due to the limitations of this study the researcher couldn't cover. This study can act for advocating the rights of tribal women's health especially when gynecological cancers have been to factors like lack of awareness and hygiene, and limited access to gynaecologists [11]. The sources of awareness covered an important part of the problem that can be used to design intervention to address the issue . The findings can be used as means for advocacy to put the light on the various aspects of the gynecological cancers that currently remains unaddressed for the marginal community of tribal women.

Data Availability

Data is data available on request through ethics committee of College of Social Work, Nirmala Niketan, Mumbai University, Mumbai, India available at the email address of nn@cswnn.edu.in

Conflicts of Interest

The study represents no conflict of interest which includes financial relationships, personal relationships or rivalries, academic competition, and intellectual beliefs.

Funding Statement

No funding was secured for the study.

Acknowledgments

Dr Rama Joshi, Director, Fortis Memorial Research Institute, Gurugram, India and Head of the Department of Gynecology Oncology was the key expert in designing the tool and providing her expertise throughout the study.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018 09 12;68(6):394-424. https://doi.org/10.3322/caac.21492
2. Uma Devi K. Current status of gynecological cancer care in India. Journal of Gynecologic Oncology. 2009;20(2):77. https://doi.org/10.3802/jgo.2009.20.2.77
3. "International Agency For Research On Cancer: Latest Global Data". 2018. Iarc.Fr. https://www.iarc.fr/wp-content/uploads/2018/09/pr263_E.pdf.
4. Consolidated report of hospital based cancer registries 2001-3, national cancer registry program. New Delhi: Indian Council of Medical Research; 2007..
5. Maheshwari A, Kumar N, Mahantshetty U. Gynecological cancers: A summary of published Indian data. South Asian Journal of Cancer. 2016;5(3):112. https://doi.org/10.4103/2278-330x.187575
6. Aswathy S, Reshma J, Avani D. Epidemiology of cervical cancer with special focus on India. International Journal of Women's Health. 2015 04;:405. https://doi.org/10.2147/ijwh.s50001
7. Denny L. "Cervical cancer: prevention and treatment." . Discovery medicine . 2012;14(75):125-31.
8. ICO Information Centre on HPV and cancer (Summary Report 2014-08-22).Human Papillomavirus and Related Diseases in India. 2014.
9. Aswathy S, Reshma J, Avani D. Epidemiology of cervical cancer with special focus on India. International Journal of Women's Health. 2015 04;:405. https://doi.org/10.2147/ijwh.s50001
10. Travasso C. Prevalence of HPV is high among Indian tribal girls and young women, study finds. BMJ. 2015 05 18;350(may18 6):h2692-h2692. https://doi.org/10.1136/bmj.h2692
11. Dey S, Pahwa P, Mishra A, Govil J, Dhillon PK. Reproductive Tract infections and Premalignant Lesions of Cervix: Evidence from Women Presenting at the Cancer Detection Centre of the Indian Cancer Society, Delhi, 2000–2012. The Journal of Obstetrics and Gynecology of India. 2016 03 11;66(S1):441-451. https://doi.org/10.1007/s13224-015-0819-1.

DOI:10.31557/APJCC.2020.5.2.119

REVIEW

The Role of 18F-FDG-PET/CT Scan in the Management of Multiple Myeloma

Shirin Haghighat

Shiraz University of Medical Science, Hematology and Medical Oncology Department, Shiraz, Iran.

Abstract

Bone lesion is a myeloma-defining event which is reported in 80% of multiple myeloma patients. Imaging of bone is essential in the evaluation of pattern and extent of bone involvement. Recently, whole body X ray (WBXR) has been replaced by more accurate imaging such as whole body MRI and FDG-PET/CT scan. This review article provides the advantages and role of PET/CT scan in the diagnosis and management of multiple myeloma patients. Generally, PET/CT in diagnosis of bone involvement of newly diagnosed myeloma patients is more sensitive than WBXR. The prognostic value of PET/CT in newly diagnosed patients has been described as well. Different studies have demonstrated that several PET parameters such as the number of focal lesions (FL), SUVmax and extramedullary disease (EMD) may affect the outcome of multiple myeloma patients. Interstingely, the main role of PET/CT in myeloma patients is treatment response monitoring and to some extent assessment of MRD. PET/CT appears to be superior than MRI in the evaluation of response due to its ability in differentiating active lesion from negative one.

Keywords: Multiple myeloma- PET- prognosis and treatment

Asian Pac J Cancer Care, **5 (2)**, 119-123

Submission Date: 04/29/2020 Acceptance Date: 06/19/2020

Introduction

Infiltration and expansion of malignant monoclonal plasma cells, basically in the bone marrow causes multiple myeloma (MM) [1]. As indicated by the global cancer statistics 2018, MM represented 0.9% of all new malignancies and 1.1% of leading causes of cancer death worldwide in 2018 [2]. According to the global burden of multiple myeloma study, age-standardized incidence and mortality were highest in the Australasian, North American, and Western European regions and lowest in Asia, Oceania, and sub-Saharan Africa [3]. It is a proven fact that multiple myeloma develops from an asymptomatic premalignant condition clinically identified as monoclonal gammopathy of undetermined significance (MGUS) [4-5]. Hypercalcemia, anemia, renal function impairment, and bone lesions are classic CRAB features which are currently established diagnostic criteria for symptomatic MM [6]. Recently, International Myeloma Working Group has revised the criteria of diagnosis of MM and has mentioned the use of computed tomography (CT) scan and positron emission tomography (PET) scanning in addition to skeletal radiography to diagnose lytic bone lesions [7]. The most accepted staging system in patients affected by MM includes the international staging system (ISS) and Durie–Salmon staging system (DSS) [8]. The ISS is an easy risk scoring system that includes two parameters; serum β_2-microglobulin level and serum albumin level. This risk stratification system which is established in 2005, classified MM patients into three prognostic groups with different overall survival [9]. DSS predicts survival on the base of four parameters; M component production rate, hemoglobulin concentration, calcium value and the number of lytic bone lesions on X-ray [10]. Interpretation of bone lesions on X-rays have some limitation, so new Durie-salmon plus staging system was developed in 2006 which integrated new imaging techniques such as whole-body CT scan, magnetic resonance imaging (MRI) and whole-body FDG-PET scanning into anatomic and functional staging [11]. Bone involvement is one of the most frequent presentation of multiple myeloma, observed in about

Corresponding Author:
Dr. Shirin Haghighat
Shiraz University of Medical Science, Hematology and Medical Oncology, Shiraz, Iran.
Email: sh.haghighat2010@yahoo.com

two-thirds of patients at the time of diagnosis and in approximately all patients in the course of their diseases [12]. Therefore imaging could be an essential part of the approach to multiple myeloma for detection of lytic bone lesions and identification of extramedullary disease to demonstrate the need for early treatment [12]. Although plain X-rays have been easily available skeletal surveys for a long time, it has a major limitation. Osteolytic bone lesions could be only detectable if at least 30% of trabecular bone is lost [13-14]. More sensitive imaging modalities such as CT, MRI, and PET can be used as an alternative to detect lytic bone lesions at the earlier stage of disease efficiently [15]. The European Society of Medical Oncology (ESMO) and European Myeloma Network (EMN) guidelines recommend a whole-body low dose CT scan as a new standard imaging for the detection of osteolytic bone lesions. These guidelines also recommend MRI and FDG-PET/CT scans to provide more details according to their availability [16-17]. In this article, I focus primarily on the role of FDG-PET/CT scan in the diagnosis, staging, therapy assessment and detection of minimal residual disease.

Diagnostic value of FDG-PET CT scan

PET/CT scan by using FDG as a radiotracer can detect the glucose hypermetabolism of medullary and intramedullary lesions and gives properly both morphological and functional information [14-18]. It is widely accepted that whole-body PET/CT and MRI are equal in detecting focal bone lesions at diagnosis, however, MRI is more powerful at detecting diffuse disease and PET/CT is more reliable in detecting extramedullary diseases [19-20-21)]. National Oncologic PET Registry (NOPR) has recently published the impact of PET/CT on intended management of 16 different cancer types which reported the highest frequency of a change in intended treatment in multiple myeloma (48.7%) compared to other types of cancers [22]. A high impact of PET on the management of patients with plasma cell disorder has been also demonstrated in a Canadian retrospective study with a change in the planned approach in more than 2/3 of patients [15]. A significant correlation between 18F-FDG parameters (SUVs and kinetics) and bone marrow plasma cell infiltration was approved in 40 patients with primary symptomatic multiple myeloma by a German study in 2015 [23]. Several studies have illustrated the sensitivity and specificity ranging from 75% to 100% in detecting lytic bone lesions and staging by PET/CT scan [24-25]. In patients with nonsecretory multiple myeloma who do not have any measurable parameters, more sensitive skeletal survey methods like PET/CT scan can assess the stage of the disease [26]. Another condition in which PET/CT scan continues to be a considerable topic is solitary plasmacytoma, a single bone or soft tissue mass of clonal plasma cell with no or small bone marrow plasmacytosis. A panel of expert European hematologists recommended PET/CT or MRI, at least one of them, as a mandatory imaging modalitiy in a case of solitary plasmacytoma to exclude the presence of additional lesions [27]. The last IMWG guideline also recommends the PET/CT scan for the first evaluation of patients with solitary extramedullary plasmacytoma [1].

The role of PET/CT in the assessment of prognosis

Several studies have shown the prognostic value of PET/CT in patients with smoldering multiple myeloma (SMM) and MM. A prospective study of a cohort of 120 patients with SMM has shown the probability of progression to MM in 2 years is 58% for patients with positive PET/CT versus 33% for PET/CT-negative patients [28]. Siontis et al. also showed that patients with SMM who have positive PET/CT scans are at higher (75%) risk of progression to symptomatic MM within 2 years [29]. These studies support the use of PET/CT scan to identifying the patients with SMM at higher risk of progression to symptomatic MM who are probably candidates for early initiation of treatment. Bartel et al. demonstrated the impact of PET/CT parameters such as the number of focal lesions (FL), presence of extramedullary disease (EMD), and SUV of lesions on the survival outcome of patients affected by MM [30]. Another Italian study has prospectively evaluated the prognostic significance of the same PET/CT parameters in patients with MM. This study revealed that FL≥3, SUV>4.2, and EMD in PET/CT associated with shorter PFS and OS [31].

Volume-based PET parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been used to measure the metabolic activity of the tumor. Fonti et al. reviewed retrospectively medical data of 47 patients with newly diagnosed untreated MM and measured MTV, determined by FDG-PET/CT. They demonstrated the value of MTV in the prediction of PFS and OS in myeloma patients [32]. Similarly, another study by McDonald et al. found the useful survival implication of MTV and TLG. They also demonstrated the superiority of these volumetric measurements on the number and SUV of focal lesions in the prediction of OS and PFS [33]. A Chinese study has found the correlation between ki-67 expression and increase in FDG uptake in PET/CT in patients with EMM. They have also shown the prognostic implication of combination of ki-67 expression and SUVmax in PET in EMM patients [34]. In another study, Cengiz et al. reported that there was a significant correlation between bone marrow FDG uptake and percentage of CD38- and CD-138 expressing plasma cell. They also revealed the correlation between FDG uptake and some prognostically relevant laboratory parameters such as β2M and CRP [35]. As well the correlation between SUVmax in bone lesions and clinical parameters related to tumor burden such as high M protein, plasma cell >20% in bone marrow, β2M>3.5mg/dl, hypercalcemia at the onset of disease, and increased LDH was reported by Li et al [36].

Evaluation of treatment response with F-FDG PET/CT

18F-FDG PET/CT is a superior imaging modality to evaluate the response to treatment because it can distinguish between active and inactive lesions [12]. Several studies have demonstrated that post-treatment PET negativity correlates with a significant response to

therapy. They have found the correlation between FDG suppression before transplantation and better outcome [30-31]. Caldarrela et al. have confirmed the usefulness of FDG PET/CT in assessing the response to treatment in a systematic review of 10 studies involving 690 patients with multiple myeloma and solitary plasmacytoma. They also found that response to treatment could be shown by FDG-PET earlier than other imaging tools such as MRI and whole-body X-ray [37]. Another retrospective study of 282 patients with MM showed that in patients achieving conventionally complete response (CR), positive PET associated with two times higher risk of progression compared to negative PET [38]. Several studies have compared FDG-PET with whole-body MRI in post-treatment setting to provide information about the persistent disease. They confirmed that MRI may have falsely positive results due to persistent signal abnormalities in non-active lesions. While the unique role of PET/CT in the evaluation of response to treatment has been proved [39-40]. Another study on 19 patients with multiple myeloma has demonstrated that FDG-PET before and after the first cycle of chemotherapy may be helpful to identify the patients who would respond to this chemotherapy [41]. In recent years, modern combination therapies in newly diagnosed MM patients have improved the depth of response and have increased the minimal residual disease negativity [42]. several meta-analysis and reviews have shown that MRD negativity associated with increased OS and PFS [43-44]. Therefore, improving the currently employed assays to detect the MRD may be considered one of the major goals in the management of MM patients. Different studies have evaluated the complementary role of PET/CT to existing methods such as bone marrow techniques, multiparameter flow cytometry (MFC) and next-generation sequencing (NGS). They reported higher OS in MRD-/PET- or MRD+/PET- patients (4-year OS 94.2 and 100 % respectively) compared to PET+ patients (4-year OS 73.8%) [45].

What are the limitations of the FDG-PET scan?

Although the usefulness of PET/CT in diagnosis, staging and treatment monitoring has been suggested by several studies some reviews have demonstrated the limitations of PET/CT in this issue. Limited availability and higher cost compared to conventional imaging are the major causes of less application of PET/CT in the diagnosis and management of multiple myeloma in some institutes. False-positive results may be observed in different inflammatory conditions (such as thyroiditis, inflammatory bowel disease, and esophagitis), chemotherapy within the past 4 weeks, and radiotherapy within the past 2-3 months. Patients who received granulocyte colony-stimulating factors (GCSF) recently may show false positive uptake of FDG in the bone marrow [46]. Post-surgical and fracture areas can be other important causes of false-positive results in the FDG-PET scan [21]. False-negative results including hyperglycemia and recent use of high dose glucocorticoids are other limitations of FDG-PET for evaluation of patients with multiple myeloma. Sequestration phenomenon may be a potential pitfall in interpreting the post-therapy FDG-PET in myeloma patients. Heavily bone marrow infiltration by tumoral cells causes sequestration of 18F-FDG tracer in the bone marrow and lower availability of tracer to detect other sites of active disease. Successful treatment of bone marrow infiltration leads to an increase in the metabolic activity of residual disease then misinterpretation of the residual lesions as a progressive disease [47].

In conclusion, this mini-review shows that available evidence on the value of PET/CT in diagnosis, staging, prognosis and response monitoring is promising. PET/CT can detect myeloma bone lesions with a sensitivity higher than WBXR and comparable to MRI. It may also provide significant prognostic information in smoldering myeloma and solitary plasmacytoma. Interestingly, PET/CT could be a useful tool to monitor the treatment response due to its ability to detect the metabolic activity in lesions.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Hillengass J, Usmani S, Rajkumar SV, Durie BGM, Mateos M, Lonial S, Joao C, Anderson KC, García-Sanz R, Riva E, Du J, van de Donk N, Berdeja JG, Terpos E, Zamagni E, Kyle RA, San Miguel J, Goldschmidt H, Giralt S, Kumar S, Raje N, Ludwig H, Ocio E, Schots R, Einsele H, Schjesvold F, Chen W, Abildgaard N, Lipe BC, Dytfeld D, Wirk BM, Drake M, Cavo M, Lahuerta JJ, Lentzsch S. International myeloma working group consensus recommendations on imaging in monoclonal plasma cell disorders. The Lancet Oncology. 2019 06;20(6):e302-e312. https://doi.org/10.1016/s1470-2045(19)30309-2
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018 09 12;68(6):394-424. https://doi.org/10.3322/caac.21492
3. Cowan AJ, Allen C, Barac A, Basaleem H, Bensenor I, Curado MP, Foreman K, Gupta R, Harvey J, Hosgood HD, Jakovljevic M, Khader Y, Linn S, Lad D, Mantovani L, Nong VM, Mokdad A, Naghavi M, Postma M, Roshandel G, Shackelford K, Sisay M, Nguyen CT, Tran TT, Xuan BT, Ukwaja KN, Vollset SE, Weiderpass E, Libby EN, Fitzmaurice C. Global Burden of Multiple Myeloma. JAMA Oncology. 2018 09 01;4(9):1221. https://doi.org/10.1001/jamaoncol.2018.2128
4. Rajkumar SV, Kumar S. Multiple Myeloma: Diagnosis and Treatment. Mayo Clinic Proceedings. 2016 01;91(1):101-119. https://doi.org/10.1016/j.mayocp.2015.11.007
5. Rajkumar SV. Evolving diagnostic criteria for multiple myeloma. Hematology. 2015 Dec 05;2015(1):272-278. https://doi.org/10.1182/asheducation-2015.1.272
6. Hussain A, Almenfi HF, Almehdewi AM, Hamza MS, Bhat MS, Vijayashankar NP. Laboratory Features of Newly Diagnosed Multiple Myeloma Patients. Cureus. 2019 05 22;. https://doi.org/10.7759/cureus.4716
7. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos M, Kumar S, Hillengass J, Kastritis E, Richardson P, Landgren O, Paiva B, Dispenzieri A, Weiss B, LeLeu X, Zweegman S, Lonial S, Rosinol L, Zamagni E, Jagannath S, Sezer O, Kristinsson SY, Caers J, Usmani SZ, Lahuerta JJ,

Johnsen HE, Beksac M, Cavo M, Goldschmidt H, Terpos E, Kyle RA, Anderson KC, Durie BGM, Miguel JFS. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. The Lancet Oncology. 2014 Nov;15(12):e538-e548. https://doi.org/10.1016/s1470-2045(14)70442-5

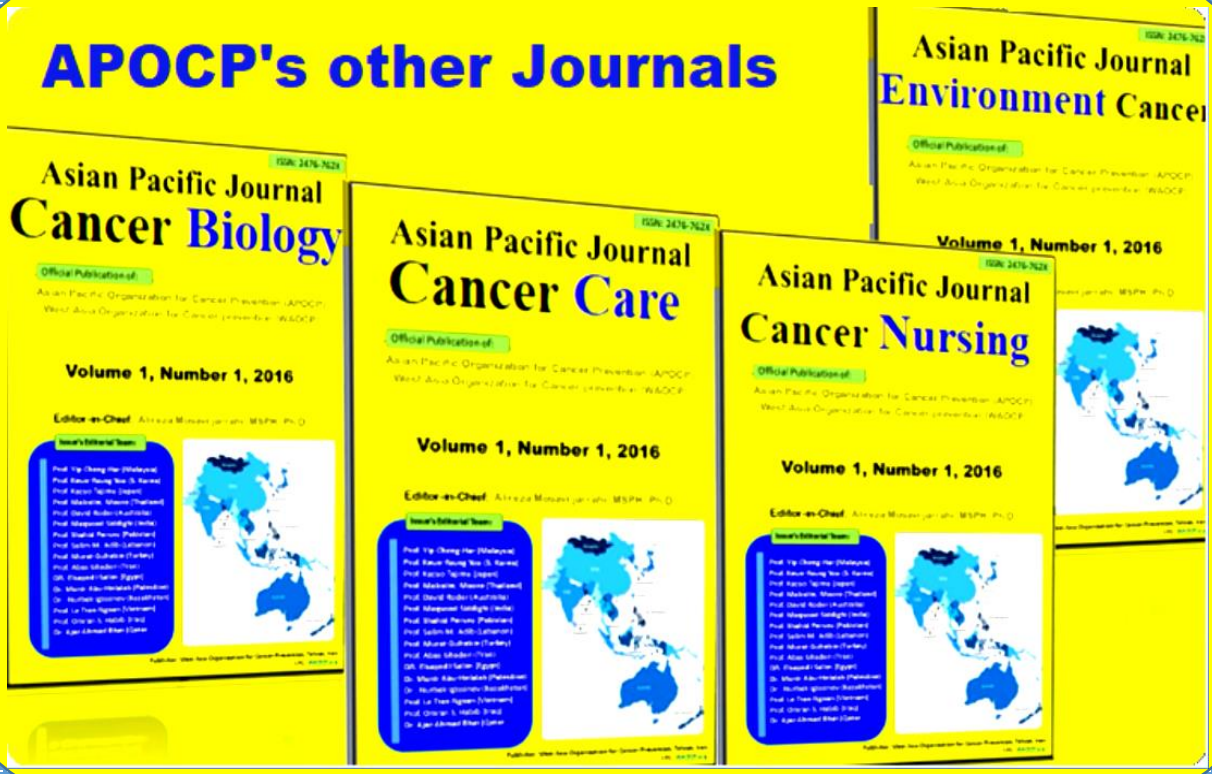
8. Deng S, Zhang B, Zhou Y, Xu X, Li J, Sang S, Zhang W. The Role of18F-FDG PET/CT in Multiple Myeloma Staging according to IMPeTUs: Comparison of the Durie–Salmon Plus and Other Staging Systems. Contrast Media & Molecular Imaging. 2018 07 30;2018:1-9. https://doi.org/10.1155/2018/4198673
9. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, Richardson P, Caltagirone S, Lahuerta JJ, Facon T, Bringhen S, Gay F, Attal M, Passera R, Spencer A, Offidani M, Kumar S, Musto P, Lonial S, Petrucci MT, Orlowski RZ, Zamagni E, Morgan G, Dimopoulos MA, Durie BG, Anderson KC, Sonneveld P, San Miguel J, Cavo M, Rajkumar SV, Moreau P. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. Journal of Clinical Oncology. 2015 09 10;33(26):2863-2869. https://doi.org/10.1200/jco.2015.61.2267
10. Hari PN, Zhang M, Roy V, Pérez WS, Bashey A, To LB, Elfenbein G, Freytes CO, Gale RP, Gibson J, Kyle RA, Lazarus HM, McCarthy PL, Milone GA, Pavlovsky S, Reece DE, Schiller G, Vela-Ojeda J, Weisdorf D, Vesole D. Is the international staging system superior to the Durie–Salmon staging system? A comparison in multiple myeloma patients undergoing autologous transplant. Leukemia. 2009 03 26;23(8):1528-1534. https://doi.org/10.1038/leu.2009.61
[11. Durie BG. The role of anatomic and functional staging in myeloma: Description of Durie/Salmon plus staging system. European Journal of Cancer. 2006 07;42(11):1539-1543. https://doi.org/10.1016/j.ejca.2005.11.037
12. Zamagni E, Tacchetti P, Cavo M. Imaging in multiple myeloma: How? When?. Blood. 2019 02 14;133(7):644-651. https://doi.org/10.1182/blood-2018-08-825356
13. Derlin T. Imaging of multiple myeloma: Current concepts. World Journal of Orthopedics. 2014;5(3):272. https://doi.org/10.5312/wjo.v5.i3.272
14. Kosmala A, Bley T, Petritsch B. Imaging of Multiple Myeloma. RöFo - Fortschritte auf dem Gebiet der Röntgenstrahlen und der bildgebenden Verfahren. 2019 06 11;191(09):805-816. https://doi.org/10.1055/a-0864-2084
15. Shachar B, Prica A, Anconina R, Hawsawy A, MacCrostie P, Langer D, Metser U. Impact of 18F-fluorodeoxyglucose PET/CT in the management of patients with plasma cell disorders. Nuclear Medicine Communications. 2020 01;41(1):34-39. https://doi.org/10.1097/mnm.0000000000001113
16. Moreau P, San Miguel J, Sonneveld P, Mateos M, Zamagni E, Avet-Loiseau H, Hajek R, Dimopoulos M, Ludwig H, Einsele H, Zweegman S, Facon T, Cavo M, Terpos E, Goldschmidt H, Attal M, Buske C. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2017 07;28:iv52-iv61. https://doi.org/10.1093/annonc/mdx096
17. Caers J, Garderet L, Kortüm KM, O'Dwyer ME, van de Donk NW, Binder M, Dold SM, Gay F, Corre J, Beguin Y, Ludwig H, Larocca A, Driessen C, Dimopoulos MA, Boccadoro M, Gramatzki M, Zweegman S, Einsele H, Cavo M, Goldschmidt H, Sonneveld P, Delforge M, Auner HW, Terpos E, Engelhardt M. European Myeloma Network recommendations on tools for the diagnosis and monitoring of multiple myeloma: what to use and when. Haematologica. 2018 08 31;103(11):1772-1784. https://doi.org/10.3324/haematol.2018.189159
18. Messiou C, Kaiser M. Whole-Body Imaging in Multiple Myeloma. Magnetic Resonance Imaging Clinics of North America. 2018 Nov;26(4):509-525. https://doi.org/10.1016/j.mric.2018.06.006
19. van Lammeren-Venema D, Regelink JC, Riphagen II, Zweegman S, Hoekstra OS, Zijlstra JM. 18F-fluoro-deoxyglucose positron emission tomography in assessment of myeloma-related bone disease: A systematic review. Cancer. 2011 09 01;118(8):1971-1981. https://doi.org/10.1002/cncr.26467
20. Moreau P, Attal M, Caillot D, Macro M, Karlin L, Garderet L, Facon T, Benboubker L, Escoffre-Barbe M, Stoppa A, Laribi K, Hulin C, Perrot A, Marit G, Eveillard J, Caillon F, Bodet-Milin C, Pegourie B, Dorvaux V, Chaleteix C, Anderson K, Richardson P, Munshi NC, Avet-Loiseau H, Gaultier A, Nguyen J, Dupas B, Frampas E, Kraeber-Bodere F. Prospective Evaluation of Magnetic Resonance Imaging and [18F]Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography at Diagnosis and Before Maintenance Therapy in Symptomatic Patients With Multiple Myeloma Included in the IFM/DFCI 2009 Trial: Results of the IMAJEM Study. Journal of Clinical Oncology. 2017 09 01;35(25):2911-2918. https://doi.org/10.1200/jco.2017.72.2975
21. Sachpekidis C, Goldschmidt H, Dimitrakopoulou-Strauss A. Positron Emission Tomography (PET) Radiopharmaceuticals in Multiple Myeloma. Molecules. 2019 Dec 29;25(1):134. https://doi.org/10.3390/molecules25010134
22. Hillner BE, Siegel BA, Shields AF, Liu D, Gareen IF, Hunt E, Coleman RE. Relationship Between Cancer Type and Impact of PET and PET/CT on Intended Management: Findings of the National Oncologic PET Registry. Journal of Nuclear Medicine. 2008 Nov 07;49(12):1928-1935. https://doi.org/10.2967/jnumed.108.056713
23. Sachpekidis C, Mai E, Goldschmidt H, Hillengass J, Hose D, Pan L, et al. 18F-FDG Dynamic PET/CT in Patients with Multiple Myeloma Patterns of Tracer Uptake and Correlation With Bone Marrow Plasma Cell Infiltration Rate . Clin Nucl Med. 2015;40:e300-e307.
24. Zamagni E, Cavo M. The role of imaging techniques in the management of multiple myeloma. British Journal of Haematology. 2012 08;:n/a-n/a. https://doi.org/10.1111/bjh.12007
25. Bailly C, Leforestier R, Jamet B, Carlier T, Bourgeois M, Guérard F, et al. PET Imaging for Initial Staging and Therapy Assessment in Multiple Myeloma Patients. Int. J. Mol. Sci. 2017;18:445.
26. Corso A, Mangiacavalli S. NON-SECRETORY MYELOMA: READY FOR A NEW DEFINITION?. Mediterranean Journal of Hematology and Infectious Diseases. 2017 08 18;9(1):e2017053. https://doi.org/10.4084/mjhid.2017.053
27. Caers J, Paiva B, Zamagni E, Leleu X, Bladé J, Kristinsson SY, Touzeau C, Abildgaard N, Terpos E, Heusschen R, Ocio E, Delforge M, Sezer O, Beksac M, Ludwig H, Merlini G, Moreau P, Zweegman S, Engelhardt M, Rosiñol L. Diagnosis, treatment, and response assessment in solitary plasmacytoma: updated recommendations from a European Expert Panel. Journal of Hematology & Oncology. 2018 01 16;11(1). https://doi.org/10.1186/s13045-017-0549-1
28. Zamagni E, Nanni C, Gay F, Pezzi A, Patriarca F, Bellò M, Rambaldi I, Tacchetti P, Hillengass J, Gamberi B, Pantani L, Magarotto V, Versari A, Offidani M, Zannetti B, Carobolante F, Balma M, Musto P, Rensi M, Mancuso K, Dimitrakopoulou-Strauss A, Chauviè S, Rocchi S, Fard N, Marzocchi G, Storto G, Ghedini P, Palumbo A, Fanti S,

Cavo M. 18F-FDG PET/CT focal, but not osteolytic, lesions predict the progression of smoldering myeloma to active disease. Leukemia. 2015 Oct 22;30(2):417-422. https://doi.org/10.1038/leu.2015.291
29. Siontis B, Kumar S, Dispenzieri A, Drake MT, Lacy MQ, Buadi F, Dingli D, Kapoor P, Gonsalves W, Gertz MA, Rajkumar SV. Positron emission tomography-computed tomography in the diagnostic evaluation of smoldering multiple myeloma: identification of patients needing therapy. Blood Cancer Journal. 2015 Oct;5(10):e364-e364. https://doi.org/10.1038/bcj.2015.87
30. Bartel TB, Haessler J, Brown TLY, Shaughnessy JD, van Rhee F, Anaissie E, Alpe T, Angtuaco E, Walker R, Epstein J, Crowley J, Barlogie B. F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma. Blood. 2009 09 03;114(10):2068-2076. https://doi.org/10.1182/blood-2009-03-213280
31. Zamagni E, Patriarca F, Nanni C, Zannetti B, Englaro E, Pezzi A, Tacchetti P, Buttignol S, Perrone G, Brioli A, Pantani L, Terragna C, Carobolante F, Baccarani M, Fanin R, Fanti S, Cavo M. Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with up-front autologous transplantation. Blood. 2011 Dec 01;118(23):5989-5995. https://doi.org/10.1182/blood-2011-06-361386
32. Fonti R, Larobina M, Del Vecchio S, De Luca S, Fabbricini R, Catalano L, Pane F, Salvatore M, Pace L. Metabolic Tumor Volume Assessed by 18F-FDG PET/CT for the Prediction of Outcome in Patients with Multiple Myeloma. Journal of Nuclear Medicine. 2012 Oct 15;53(12):1829-1835. https://doi.org/10.2967/jnumed.112.106500
33. McDonald JE, Kessler MM, Gardner MW, Buros AF, Ntambi JA, Waheed S, van Rhee F, Zangari M, Heuck CJ, Petty N, Schinke C, Thanendrarajan S, Mitchell A, Hoering A, Barlogie B, Morgan GJ, Davies FE. Assessment of Total Lesion Glycolysis by 18 F FDG PET/CT Significantly Improves Prognostic Value of GEP and ISS in Myeloma. Clinical Cancer Research. 2016 Oct 03;23(8):1981-1987. https://doi.org/10.1158/1078-0432.ccr-16-0235
34. Li Q, Ma J, Li H, Xu W, Cao Z, Liu S, Chen L, Gao S, Yan T, Li D, Wang X, Yue Y, Zhao Z, Wang X, Yang H, Zhao H, Yu Y, Zhang Y, Fan F, Wang Y. Correlation Between Uptake of 18F-FDG During PET/CT and Ki-67 Expression in Patients Newly Diagnosed With Multiple Myeloma Having Extramedullary Involvement. Technology in Cancer Research & Treatment. 2019 01 01;18:153303381984906. https://doi.org/10.1177/1533033819849067
35. Cengiz A, Arda HÜ, Döğer F, Yavaşoğlu İ, Yürekli Y, Bolaman AZ. Correlation between baseline 18F-FDG PET/CT findings and CD38, CD138 expressing myeloma cells in bone marrow and clinical parameters in patiens with multiple myeloma. Turkish Journal of Hematology. 2018 05 28;. https://doi.org/10.4274/tjh.2017.0372
36. Li Y, Liu J, Huang B, Chen M, Diao X, Li J. Application of PET/CT in treatment response evaluation and recurrence prediction in patients with newly-diagnosed multiple myeloma. Oncotarget. 2016 08 19;8(15):25637-25649. https://doi.org/10.18632/oncotarget.11418
37. Caldarella C, Treglia G, Isgrò MA, Treglia I, Giordano A. The Role of Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography in Evaluating the Response to Treatment in Patients with Multiple Myeloma. International Journal of Molecular Imaging. 2012;2012:1-6. https://doi.org/10.1155/2012/175803
38. Zamagni E, Nanni C, Mancuso K, Tacchetti P, Pezzi A, Pantani L, Zannetti B, Rambaldi I, Brioli A, Rocchi S, Terragna C, Martello M, Marzocchi G, Borsi E, Rizzello I, Fanti S, Cavo M. PET/CT Improves the Definition of Complete Response and Allows to Detect Otherwise Unidentifiable Skeletal Progression in Multiple Myeloma. Clinical Cancer Research. 2015 06 15;21(19):4384-4390. https://doi.org/10.1158/1078-0432.ccr-15-0396
39. Derlin T, Peldschus K, Münster S, Bannas P, Herrmann J, Stübig T, Habermann CR, Adam G, Kröger N, Weber C. Comparative diagnostic performance of 18F-FDG PET/CT versus whole-body MRI for determination of remission status in multiple myeloma after stem cell transplantation. European Radiology. 2012 07 29;23(2):570-578. https://doi.org/10.1007/s00330-012-2600-5
40. Kumar S, Glazebrook KN, Broski SM. Fludeoxyglucose F 18 PET/Computed Tomography Evaluation of Therapeutic Response in Multiple Myeloma. PET Clinics. 2019 07;14(3):391-403. https://doi.org/10.1016/j.cpet.2019.03.006
41. Dimitrakopoulou-Strauss A, Hoffmann M, Bergner R, Uppenkamp M, Haberkorn U, Strauss LG. Prediction of Progression-Free Survival in Patients With Multiple Myeloma Following Anthracycline-Based Chemotherapy Based on Dynamic FDG-PET. Clinical Nuclear Medicine. 2009 09;34(9):576-584. https://doi.org/10.1097/rlu.0b013e3181b06bc5
42. Lonial S, Anderson KC. Association of response endpoints with survival outcomes in multiple myeloma. Leukemia. 2013 07 19;28(2):258-268. https://doi.org/10.1038/leu.2013.220
43. Landgren O, Devlin S, Boulad M, Mailankody S. Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: a meta-analysis. Bone Marrow Transplantation. 2016 09 05;51(12):1565-1568. https://doi.org/10.1038/bmt.2016.222
44. Romano A, Palumbo GA, Parrinello NL, Conticello C, Martello M, Terragna C. Minimal Residual Disease Assessment Within the Bone Marrow of Multiple Myeloma: A Review of Caveats, Clinical Significance and Future Perspectives. Frontiers in Oncology. 2019 08 20;9. https://doi.org/10.3389/fonc.2019.00699
45. Alonso R, Cedena MT, Gómez-Grande A, Ríos R, Moraleda JM, Cabañas V, Moreno MJ, López-Jiménez J, Martín F, Sanz A, Valeri A, Jiménez A, Sánchez R, Lahuerta JJ, Martínez-López J. Imaging and bone marrow assessments improve minimal residual disease prediction in multiple myeloma. American Journal of Hematology. 2019 06 09;94(8):853-861. https://doi.org/10.1002/ajh.25507
46. Dammacco F, Rubini G, Ferrari C, Vacca A, Racanelli V. 18F-FDG PET/CT: a review of diagnostic and prognostic features in multiple myeloma and related disorders. Clinical and Experimental Medicine. 2014 09 14;15(1):1-18. https://doi.org/10.1007/s10238-014-0308-3
47. Sundaram S, Driscoll J, Fernandez-Ulloa M, Lima M, Malek E. FDG PET imaging in multiple myeloma: implications for response assessments in clinical trials. Am J Nucl Med Mol Imaging. 2018;8(6):421-7.

APOCP's historical prospect:

The 9th GA and Sci. Conference of APOCP, Jeju, Korea, 2018

APOCP's other Journals



Asia Pacific Journal of Cancer Care (APJCC) is published by the West Asia Organization for Cancer prevention (the APOCP's West Asia Chapter). Visit our website at: http://waocp.org or http://apocp.info