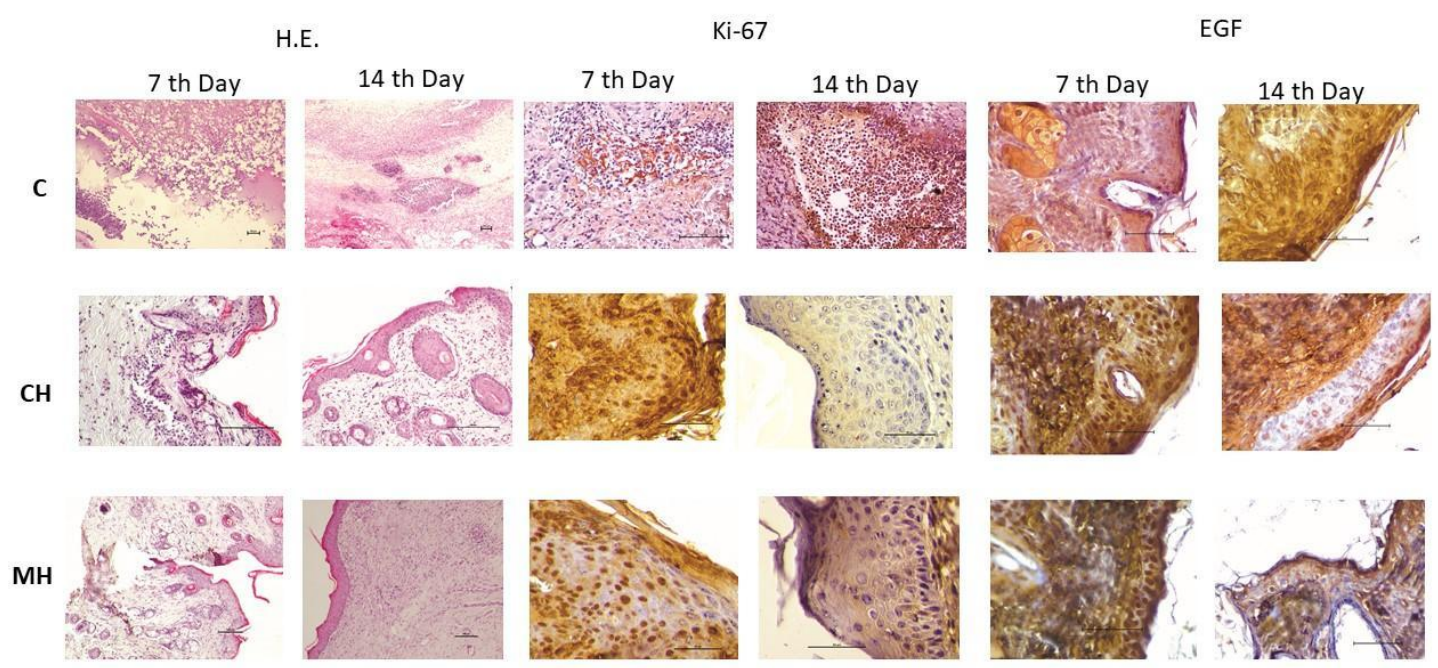


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Treatment results and patient characteristics for breast cancer patients older than 70 Years

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ABSTRACT

Objective: The incidence of breast cancer (BC) subtypes varies according to age, and its treatment is more strenuous and requires much more attention in advanced ages. The aim of this study is to investigate patient characteristics and treatment results respectively for patients older than 70 years.

Materials and Methods: In this study, we examined 188 elderly BC patients treated in our hospital, at March 2008 - November 2019. Patient characteristics and demographics were investigated from patients' files retrospectively.

Results: Mean age of the patients was 74.3 ± 4 years (All female). The presence of comorbid diseases was 76.1%. Major histology was invasive ductal carcinoma in 72.9% and mostly grade 2 differentiated, and the majority of patients were T2 size (58.5%). Oestrogen receptor (OR) positivity was seen in 83%, Progesterone receptor (PR) positivity in 72.3% of patients and cerb2 positivity in 16.5%. Luminal B (47.9%) was the most common in molecular subgroup analysis. Patients with lymph node involvement (N1 33%; N2, 19.1%; N3, 6.9%) were higher than those without involvement (34%). Surgery type was modified radical mastectomy (MRM) for 51.6%, breast conserving surgery (BCS) for 39.4 % and lumpectomy for 7.4%. In a median follow-up time was 53.9 (9-101) months, local recurrence was seen in 5 (2.7%) patients and distant metastasis was developed in 16 (8.5%) patients. The median overall survival was worse in those with MRM than those with BSC ($p=0.006$). In multivariate logistic regression analysis, only found that lymph node positivity was an independent risk factor for metastasis (HR; 4.15, 95% CI:1.019-16.933, $P=0.047$).

Conclusion: While it was observed that the most important risk factor for metastasis risk in elderly patients was lymph node positivity; The hormonal status and her2 conditions were not affected in terms of metastasis. It was thought that tumor clinical course and relapse may differ in the elderly population compared to general BC patients.

Key words: Breast cancer, elderly, treatment, comorbidity, survival

INTRODUCTION

Elderly women with breast cancer (BC) are increasing rapidly because of the rising average life expectancy of the population. Nearly 50 % women diagnosed BC are > 65 years old (1). Treatment options of BC are generally substandard in older patients. There are some studies showing that tumor subtype and patient age are important prognostic factors to determine optimal treatment (2,3). Although the primary surgical approach is generally conservative in advanced age patients (4), standard surgery methods are increasing rapidly like younger patients, especially with little or no comorbidities (5-11). Although axillary dissection is controversial due to treatment morbidity in clinically negative patients (12-16), in a group of more high-risk patients who are healthy, lymph node evaluation may supply important information about adjuvant treatment options such as chemotherapy (17). Adjuvant treatment decisions such as chemotherapy, hormonotherapy, radiotherapy can change some factors including patient life expectancy, comorbidities and patient choice. In patients with breast-conserving surgery, ipsilateral tumor recurrence is reduced by postoperative adjuvant radiotherapy (18-20). On the other hand, hormone receptor-positive, axillary negative low-risk patients hormonotherapy option without radiotherapy was investigated (21).

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Since, patients with cardiovascular disease and diabetes have a high risk of Trastuzumab treatment, it is more appropriate to treat healthy, fit patients with pre-cardiac tests and cardiac monitorization (22-25).

While bone fracture and musculoskeletal disorders are more prominent in the use of aromatase inhibitors, thromboembolic events and the risk of endometrial cancer are at the forefront of the use of tamoxifen in the treatment-related side effect. Therefore, pre-treatment bone mineral density measurements and calcium/vitamin D supplements are important especially in patients receiving aromatase inhibitors (26-28).

Due to the presence of comorbid diseases in these patients, treatment toxicity due to adjuvant poly-chemotherapy is also high (29). However, factors such as life expectancy, stage of disease and expected chemotherapy benefit are also highlighted in the decision of adjuvant chemotherapy (30-32).

MATERIAL and METHODS

In this study, we examined 188 elderly BC patients respectively treated in our hospital, at March 2008-November 2019. Table 1 shows the treatment modalities of the patients. Surgery type was mastectomy for 51.6%, breast conserving surgery for 39.4% and only lumpectomy for 7.4%. Axillary dissection was performed at 67%.

Sentinal lymph node biopsy was applied for 42%. Postoperative adjuvant RT was given for 97.9%. While radiotherapy doses were 46-50 Gy in 23-25 fractions generally, hypofractionated radiotherapy was applied for 6 patients as 2.30-2.66 Gy in 16-18 fractions. Only breast or chest wall irradiation was applied for 31.9%. In addition to breast or chest wall irradiation, nodal irradiation (supraclavicular + level 3 axillary) was performed at 55.3%. Intraoperative radiotherapy was applied in two patients as 20 Gy.

Chemotherapy was given for 66.1 %. Neoadjuvant chemotherapy was given for 6 patients. Chemotherapy protocols were Adriamycin + Cyclophosphamide (AC) plus Taxane, Cyclophosphamide + Adriamycin+ 5 _fluorouracil (CAF), AC and Cyclophosphamide + Epirubicin + 5-Fluorouracil (CEF) plus Dosectaxel. AC plus Taxane was the most preferred chemotherapy protocol (60.4%). Adjuvant hormone therapy were given for 81.9%. Hormonotherapy protocols were aromatase inhibitors for 70.2%, tamoxifen for 2.1% and both of them for 2.1%.

Comorbidity was seen in 143 (76.1%) of patients due to advanced age. Comorbid diseases were detected as hypertension (62.2%), diabetes mellitus (28.7%), coronary artery disease (12.2%), chronic obstructive pulmonary disease and asthma (6.9%), thyroid dysfunction (5.9%). Apart from these diseases, hyperlipidaemia, congestive heart failure, cerebrovascular event, dysrhythmia, Alzheimer's, depression, pulmonary hypertension, hyperparathyroidism, Parkinson's and heart valve diseases were less than 5%.

The age, features of histopathology, hormone and nodal status, tumor size, types of treatment, date of progression and last outpatient control or the date of exitus were retrieved from the patients' hospital records.

RESULTS

Patient characteristics

Table 2 shows the characteristic features of the 188 patients. All female, the mean age of the patients were 74.3 years (std. deviation 4.025). The family history was present in 30 (16%) patients. Histopathology was compatible with invasive ductal carcinoma in 72.9%, mucinous carcinoma in 8%, ductal carcinoma in situ in 5.9%, papillary carcinoma in 5.3%, invasive lobular carcinoma in 4.8% patients. Tumor localization was right for 48.9%, left for 43.6%. Tumor size were T1 for 25.5%, T2 for 58.5%, T3 for 8.5% and T4 for 4.3%. The majority of patients were T2 size (58.5%). Patients with lymph node involvement (N1,33%; N2,19.1%; N3,6.9%) was higher than those without involvement (34%). Nodal status was unknown for 4.8%. Tumor stage were stage 1 for 14.9%, stage 2 for 50%, stage 3 for 29.8% and stage 4 for 1.1 %. Half of the patients were stage 2A and 2B. Histopathological grades were as following; grade 1 for 7.4%, grade 2 for 46.8 and grade 3 for 38.8%.

The surgical margin was negative in 79.8% of patients. Surgical margin positivity was present in 6.9% and less than 1 mm of surgical proximity in 6.9% of patients. Lymph node positivity was shown in 37.9% of the 79 patients with sentinel lymph node biopsy. ER positivity was present in 83%, PR positivity in 72.3% of patients and cerb2 positivity in 16.5% patients. Luminal B (47.9%) was the most common in molecular subgroup analysis. The 27.7% of patients have Luminal A, 9% of patients have basal-like, 4.8 of patients were her2 overexpressed molecular subtype.

Survival data and prognostic factors

In a median 53.9 (9-101) months follow-up, 22 patients had exitus. Graphic 1 shows the general survival of the 188 patients. Local relapse was seen in 5 (2.7%) patient, 16 (8.5%) patients also developed distant metastasis and the median life expectancy was not reached. In graphic 2, survival curves are seen according to metastasis status. Although median values were not obtained in hypertensive patients, the median OS was worse (84 vs. 95 months, P=0.08). However, the median survival in diabetic patients was similar (87 vs. 88 months, P=0.611). In the group with coronary artery disease, median overall survival (OS) was worse numerically and the difference was close to statistical signification ([79.7 (69.6-89.7) vs. not reached, P=0.078). According to hyperlipidemia, chronic obstructive pulmonary disease, asthma, histologic subtypes, nuclear grade, surgical boundary proximity or positivity, oestrogen and progesterone receptor, Her-2 status, Ki 67% (>10 vs <10%), luminal subtypes, tumor laterality (left vs right) and adjuvant chemotherapy survival was similar (P≥0.05 all). The median survival time was worse in those with MRM than those with BSC (82 ± 3.6) vs. 94 ± 2.7, p=0.006). T1 stage was again associated with good overall survival (P=0.02). OS was similar according to whether there was nodal involvement or not. Median survival in patients receiving nodal radiotherapy was worse than those without (Enel 85.3 vs. 94.1, p=0.031).

Due to the lack of median survival in the subgroups, no analysis could be done on the independent factors affecting OS and disease-free survival due to the short follow-up time and the very small number of patients who relapsed.

When the factors affecting metastasis are examined, logistic regression analysis only found that lymph node positivity was an independent risk factor for metastasis (HR:4.15, 95%CI:1.019-16.933, $p=0.047$), ER, PR, Her2 condition, surgical type, tumor size, adjuvant chemotherapy, hormone therapy, grade, comorbid diseases and age were not an independent risk factor for metastasis risk ($p>0.05$ all).

Table 1. Demographical and clinical characteristics of the patients

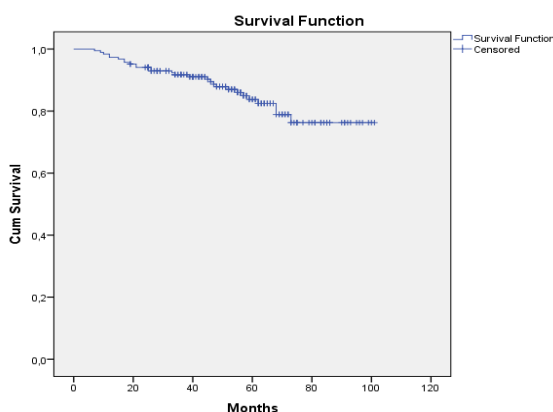
Variables	%
Age (years), mean \pm SD	74.3 \pm 4
Histological subtype	72.9
Invasive ductal carcinoma	4.8
Invasive lobular carcinoma	8
Mucinous carcinoma DCIS	5.9
Papillary carcinoma	5.3
Histopathological grade	
Grade1	7.4
Grade2	46.8
Grade3	38.8
Molecular subtypes	
Luminal A subtype	27.7
Luminal B subtype	47.9
Triple negative	9
Her2 type	4.8
Pathological stage	
Stage 1	14.9
Stage 2	50
Stage 3	29.8
Stage 4 (clinical or pathological)	1.1
Receptor Status	
ER positive	83
PR positive	72.3

SD, standard deviation, ER, oestrogen receptor; PR, progesterone receptor

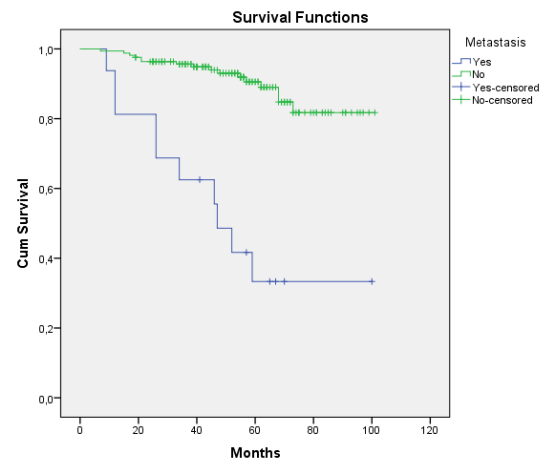
Table 2. Treatment modalities of the 188 patients

Treatment Modality	%
Mastectomy	51.6
BCS	39.4
Lumpectomy	7.4
Radiotherapy	97.9
Chemotherapy	66.1
Hormonotherapy	81.9

BCS, Breast conserving surgery



Graphic 1. Overall survival of 188 patients



Graphic 2. Overall survival according to metastasis status

DISCUSSION

Some studies showed that surgery is safe method for elderly patients, especially if they are fit and have little or no comorbidities (5-8). The International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) have recommended that patients 70 years or older should be offered the same surgery as their younger counterparts (9). Patients who had surgery had a significantly better outcome and primary hormonotherapy without surgery should be used for elderly patients with short life expectancy (10,11).

In our study, surgery type was mastectomy for 51.6%, breast conserving surgery for 39.4% and lumpectomy for 7.4%. Despite, the presence of 76.1 comorbid disease, standard surgical treatments was applied to the patients. On the other hand, the average survival time was worse in those with MRM than in those with BSC ($p=0.006$). This can be explained by the fact that patients with MRM are more advanced stage than those with BSC.

In the elderly patients, the role of axillary dissection is controversial because of the morbidity of the procedure, especially in clinically node-negative patients (12-16). NSABP -32 showed that omission of the axillary lymph node dissection in patients with clinically node-negative disease had no impact on OS and disease-free survival and regional control (16).

On the other hand, the role of sentinel lymph node biopsy has been searched with some reports. Because, in a group of more high-risk patients who are healthy, lymph node evaluation may supply important information about adjuvant treatment options such as chemotherapy (17).

In our study, approximately 50% of patients in this age group usually refer to the hospital later stage of the disease, especially stage 2A and 2B. Since the majority of patients are in advanced stages, the proportion of patients with axillary dissection is also high (67%). SLNB was administered to 79 patients who were clinically negative with axillary at the beginning of the disease, and the lymph node positivity rate was 37.9% for these groups of the patients.

In patients with breast-conserving surgery, ipsilateral tumor recurrence is reduced by post-operative adjuvant radiotherapy (18-20). Unless there is an advanced comorbid disease, adjuvant radiotherapy can be well tolerated with minimal morbidity in these patients. On the other hand, 1326 patients over 65 years of age, low risk, hormone-positive, axilla negative and hormonotherapy were retrospectively evaluated in the work of PRIME 2 (Post-operative Radiotherapy In Minimum -risk Elderly) (21). In this study, the recurrence rates in the ipsilateral breast were 1.3% in RT areas and 4.1% were not found in those who did not, while OS was not different.

In our study, BCS and lumpectomy were applied for 46.8 %; mastectomy was applied for 51.6% patients. Postoperative adjuvant radiotherapy was not given only in 4 mastectomy patients with early stage. While treatment is well tolerated in all patients, local recurrence was seen only in 5 patients (2.7%). On the other hand, survival was found to be worse in patients receiving nodal radiotherapy than those who did not, and this can be explained by the fact that patients receiving nodal radiotherapy are at a more advanced stage.

Adjuvant Trastuzumab treatment is effective in patients with Her2 over precipitation. However, patients with cardiovascular disease and diabetes have a high risk of cardiac toxicity (22-24). Therefore, it is more appropriate to treat healthy fit patients with precardiac tests and cardiac follow-up (25).

In our study, her-2 over expression was detected for 4.8% of patients and cerb-b2 was positive for 16.5 % of the patients. Adjuvant Trastuzumab treatment was applied to 21 patients. Echo, VS cardiac tests were performed to all patients before treatment. Pericarditis due to treatment were developed in 2 of patients, and cardiac tamponade was developed in one patient.

Endocrine treatment options are applied in hormone receptor-positive advanced age patients as well as in young patients. While thromboembolic events and the risk of endometrial cancer are at the forefront of the use of tamoxifen, bone fracture and musculoskeletal disorders are more prominent for aromatase inhibitors as treatment-related side effects. Therefore, pre-treatment bone mineral density measurements and calcium/vitamin D supplements are important, especially in patients receiving aromatase inhibitors (26-28).

In our study, hormonotherapy was given to most patients since receptor positivity rate is also high. Bone mineral density measurements and calcium/vitamin D supplements were done to all the patients before treatment.

Due to the presence of comorbid diseases in elderly patients, treatment toxicity due to adjuvant poly-chemotherapy is also high (29). However, factors such as life expectancy, stage of disease and expected chemotherapy benefit are also highlighted in the decision of adjuvant chemotherapy. (30,31,32). As in younger patients, poly-chemotherapy regimens are more effective (33). In the CALGB TRIAL, standard adjuvant chemotherapy with CMF or doxorubicin plus cyclophosphamide was more effective than Capecitabine alone in fit patients over 65 years (29).

In this study, chemotherapy was applied 66.1% of patients. AC plus Taxol was the most preferred protocol (60.4%) since patients applied to the hospital generally at advanced stages of the disease. Although, treatment was well tolerated in most of the patients, hepatotoxicity was seen in one patient during Taxol treatment.

In our study, 22 patients were ex during the follow-up. Distant metastasis was detected in 16 (8.5%) patients. Bone was the most common site of metastasis (4.8%). When the factors affecting metastasis were examined, it was observed that only lymph node positivity was an independent risk factor for metastasis in logistic regression analysis (p=0.047).

During the follow-up period, secondary cancers were seen in 2 patients, including melanoma in one patient and endometrial cancer in one patient after four years of the treatment.

CONCLUSION

In the present study, the disease was frequently detected at an advanced stage due to patients were applied to the hospital lately in these age groups. However, standard treatment approaches have been applied to the majority of patients and treatment was well tolerated in most of the patients. While it was observed that the most important risk factor for metastasis risk in elderly patients was lymph node positivity; hormonal status and her2 conditions were not affected in terms of metastasis. It was thought that tumor clinical course and relapse might differ in the elderly population compared to general BC patients.

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Prevalence of *Helicobacter pylori* infection in patients with Dementia who underwent Percutaneous Endoscopic Gastrostomy (PEG) and the effect of preventive single dose ceftriaxone plus pantaprazole therapy on *Helicobacter pylori* infection

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ABSTRACT

Objective: This was a retrospective study of the hospital database from April 2020 to January 2021 to reveal the rate of *Helicobacter pylori* infection among Dementia patients who underwent percutaneous endoscopic gastrostomy (PEG) procedure. Other aim of this study is examine the effect of a single dose (two grams) intravenous ceftriaxone plus pantoprazole (40 mg) before PEG procedure on *H.pylori* infection in Dementia patients.

Material and Methods: This is a retrospective observational study of hospital database from April 2020 to January 2021 examining the effect of using a single dose (two grams) of intravenous ceftriaxone plus pantoprazole (40 mg) on *H.pylori* infection in Dementia patients. A total of 77 patients, (43 (64%) of them were female) with Dementia were included whose 67 had previously been diagnosed as Dementia and underwent PEG procedure. The control group (67 subjects; 40 of them were female and the mean age was 75.8±11 years) was selected from age and gender-matched dyspeptic subjects who underwent endoscopy

Results: While the mean age in the Dementia group was 75.8±12 years, the mean age of the control group was 77.8 ±11 years (p=0.054). There were also no gender differences between groups (p=0.594).

While the mean levels of serum albumin, urea, creatinine, hemoglobin were significantly lower than control subjects (All p values were below 0.001), the mean of serum ferritin level was higher than control subjects (p<0.01). The presence of *H.pylori* on gastric biopsy specimens was significantly lower in the Dementia group compared to control subjects (19.4% versus 55.2%).

Conclusion: Our study indicated that the rate of *H.pylori* infection was lower than estimated and using single-dose intravenous ceftriaxone at a dose of 2 grams could be beneficial for treating *H.pylori* infection in patients with Dementia who faced difficulties related to lack of swallowing many drugs against *H.pylori* infection.

Keywords: *Helicobacter pylori*, Dementia, Percutaneous Endoscopic Gastrostomy, ceftriaxone, pantaprazole

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INTRODUCTION

When the pathogenesis of Dementia is examined according to epidemiological data, it has been proven that *H. pylori* play an important role in the pathogenesis. *H. pylori* is a gram-negative bacterium that causes disorders associated with the upper gastrointestinal tract (chronic gastritis, peptic ulcer, and gastric cancer).

H. pylori may initiate neurodegeneration by damaging the blood-brain barrier, cause the release of systemic proinflammatory cytokines and allowing these cytokines to easily cross the barrier. It has also been revealed that the rate of *H. pylori* infection was higher among patients with Dementia than control subjects (1,2). Percutaneous endoscopic gastrostomy (PEG) procedure, which is a minimally invasive method that provides internal nutrition with high efficiency and safety, is the method that is frequently preferred for Dementia patients. PEG application is especially recommended when malnutrition is detected while the patient is in the middle stage. Because, PEG insertion at more advanced stages cannot contribute to the lifetime of the patients. In many studies conducted so far, it has been revealed that internal nutrition has many advantages compared to parenteral nutrition (3).

In particular, internal nutrition has important contributions to human health in the regulation of intestinal microbiota and bacterial translocation events (4). Otherhand, preventive treatment with ceftriaxone before the PEG procedure has been accepted for decades to reduce the risk of peristomal infections (5).

However, there was no study involving the effect of single-dose ceftriaxone plus pantoprazole on *H. pylori* infection in patients with Dementia. Based on this, in this study, it was aimed to examine and evaluate gastric mucosal biopsy samples in patients who applied PEG in order to determine the effect of single dose of ceftriaxone plus pantoprazole on *H. pylori* infection.

MATERIAL and METHODS

This is a retrospective observational study of hospital database from April 2020 to January 2021 examining the effect of using a single dose (two grams) of intravenous ceftriaxone plus pantoprazole (40 mg) on *H.pylori* infection in Dementia patients.

Table 1. Demographic and clinical characteristics of groups

	Peg		Control		
	n	Mean (95%CI)	n	Mean (95%CI)	p
Age(year)	67	77,8 (74,7-80,9)	67	75,8 (73-78,6)	0,054
Glucose(g/dL)	67	133 (118-147)	65	121 (110-131)	0,209
AST(IU/L)	66	25 (21-29)	64	27 (20-33)	0,742
ALT(IU/L)	67	21 (16-26)	67	22 (17-27)	0,104
Total protein(g/dl)	60	5,2 (8,94-6,18)			
Albumin(g/dL)	64	3,1 (2,9-3,2)	21	4,4 (4,1-4,6)	<0,001
ALP(IU/L)	60	85 (115-94)			
GGT(U/L)	56	31 (53-36)			
Urea(mg/dL)	67	65,1 (52,5-77,7)	63	35,3 (31,7-39)	<0,001
Creatinin(mg/dL)	67	0,8 (0,66-0,95)	67	0,86 (0,8-0,92)	0,004
Calcium(mmol/L)	65	8,53 (8,91-8,72)			
WBC(mcL)	62	9,37 (8,12-10,63)	67	7,94 (7,16-8,73)	0,189
Haemoglobin(g/dL)	62	10,4 (9,9-11)	67	12,6 (12-13,2)	<0,001
Haemotocrit(%)	62	31,7 (29,8-33,6)	67	39,1 (37,5-40,7)	<0,001
Platelet(x10 ⁹ /L)	62	246 (214-278)	67	290 (214-366)	0,290
Ferritin(ng/mL)	15	220,22 (81,95-358,5)	14	62,36 (36,81-87,91)	0,010
TSH(mIU/L)	43	1,846 (1,152-2,541)	45	2,28 (1,463-3,098)	0,126
sT4(mIU/L)	42	0,989 (2,051-1,271)			
PT(sec)	64	12,4 (13,3-12,7)			
HbA1c(%)	24	5,66 (6,81-6,1)			

A total of 77 patients, (43 (64%) of them were female) with Dementia were included whose 67 had previously been diagnosed as Dementia and underwent PEG procedure. The control group (67 subjects; 40 of them were female and the mean age was 75.8±11 years) was selected from age and gender-matched dyspeptic subjects who underwent endoscopy. Patients with gastric and esophageal cancer and those who have taken proton pump inhibitors plus antibiotics before six weeks of PEG procedure were excluded. At least two gastric biopsy samples were taken from antral gastric mucosa during PEG procedure and were evaluated by pathologists in terms of the presence of *H. pylori* infection.

Statistical analyses: All statistical analyses were performed with Statistical Product and Service Solutions (SPSS) 23.0 software (SPSS, Chicago, IL, USA). Normality analysis of quantitative data was done with Kolmogorov-Smirnov test. If comparison of data that did not fit normal distribution was made with Mann Whitney U test. The comparison of qualitative data was made with Pearson Chi-square. Data were presented as mean (95% confidence interval) and n (%). Statistical significance value was accepted as p<0.05.

RESULTS

While the mean age (±SD) in the Dementia group was 75.8±12 years, the mean age of the control group was 77.8 ±11 years (p=0.054). There were also no gender differences between groups (p=0.594) (**Table-1**). While the mean levels of serum albumin, urea, creatinine, hemoglobin were significantly lower than those control subjects (All p values were below than 0.001), the mean of serum ferritin level was higher than control subjects (p<0.01). Finally, the presence of *H.pylori* on gastric biopsy specimens by histopathologic examination was significantly lower in the Dementia group compared to control subjects (19.4% versus 55.2%) (**Table-2**).

Table 2. Presence of H.pylori on gastric biopsy specimens by histopathologic examination

		Peg	Control	p
Gender	Male	24 (35,8)	27 (40,3)	0,594
	Female	43 (64,2)	40 (59,7)	
HBS	Negative	40 (97,6)		
	Positive	1 (2,4)		
antiHBS	Negative	29 (76,3)		
	Positive	9 (23,7)		
NASH	No	41 (93,2)		
	Yes	3 (6,8)		
H. pylori	No	54 (80,6)	30 (44,8)	<0,001
	Yes	13 (19,4)	37 (55,2)	
Atrophy	No	62 (92,5)	48 (71,6)	0,002
	Yes	5 (7,5)	19 (28,4)	
Metaplasia	No	58 (86,6)	65 (97)	0,028
	Yes	9 (13,4)	2 (3)	

DISCUSSION

Until the date of work, there was no report involving using single-dose intravenous ceftriaxone plus pantoprazole on H.pylori infection among patients with Dementia in the literature. We found an extremely low rate of H. pylori infection among the studied population. Current study was also revealed that using ceftriaxone plus pantoprazole before the PEG procedure could also be beneficial to treat H.pylori infection in addition to prevention of PEG-related peristomal infections in patients with Dementia.

The prevalence of Dementia increases markedly after the age of 65, and is thought to be approximately 50% at the age of 85 years. It is known that the expected human lifespan is getting longer due to advances in medicine over the years. Nevertheless, a significant increase in the prevalence of Dementia is expected in the future(6).

Dementia is generally a chronic and progressive neurodegenerative disease that causes impairment in multiple cognitive functions (with memory decline and at least one of the territory such as executive functions, language or visuospatial abilities). Apparently, an intellectual destruction, with clouding of consciousness, causing activity inabilities of daily living may occur. The patient has developed a decline in previous cognitive functions, and behavioral disorders are often added to the clinic. Depending on the nature of the disease causing Dementia. Motor, autonomic system and sleep disorders may also occur. Alzheimer's disease most commonly causes dementia syndrome when the pathophysiological changes in the central nervous system(7).

Nutritional problems often occur in patients with Dementia, especially as the disease progresses, and these patients are at risk of malnutrition. Nutritional problems that cause malnutrition are either due to trying to eat substances that are not food as a result of the loss of the ability to recognize food.

Additionally behavioral problems as agitation and disturbed eating behavior, attention deficit, impaired decision-making ability, executive dysfunction as shopping or preparing food, loss of eating skills, as well as anosmia and taste dysfunction, impaired sense of hunger and thirst, as well as refusal to eat, dysphagia, or from disruption of the entire eating process may be observed (8).

The prevalence of dysphagia in patients with Dementia ranges from 13 to 57%. Dysphagia, malnutrition, increased weight loss, aspiration pneumonia may develop, and even death may result (9).

In the middle and late stages of Dementia, dependency to caregivers develops gradually, as in the act of preparing and eating. In advanced Dementia dysphagia and indifference to eating may develop. When caregivers think that the nutritional status or fluid intake of these elderly people is inadequate, they should search for an alternative way of feeding. At this stage, unless there is a contraindicated situation, it should be recommended to continue feeding by enteral means. First of all, it should be a continuation of the recommended oral assisted feeding. However, enteral nutrition with a PEG tube is considered for adequate nutrition and hydration in individuals with advanced Dementia whose oral feeding is irreversibly declining (10).

However, according to these reports, the frequency of H. pylori in mucosal biopsies applied to these patients was found to be significantly higher than the control group. In addition to all these, there is a direct correlation between cognitive impairment and the presence of anti-H. pylori immunoglobulin G antibodies in Alzheimer's patients. In other words, between anti-H. pylori and IgG levels in cerebrospinal fluid and cognitive impairment in Alzheimer's patients are directly proportional (11).

Otherhand, treatment of *H.pylori* in patients with Dementia could be problematic due to lack of ability to take of many drugs which are given by oral route against *H pylori* infection. Thus, we conducted the presented study in this unique patient population with using single-dose ceftriaxone plus pantoprazole by intravenous route.

A recent study to explore antibiotic resistance in patients with *H.pylori* infection which was detected by a C-labeled urea breath test revealed that ceftriaxone resistance was 49.6%, and cefuroxime resistance was 25% (12).

Another invitro study in USA also revealed that minimally inhibitory concentration (MIC) of ceftriaxone against *H.pylori* infection was determined after 24 to 48 hours of incubation at 37°C by a micro broth dilution method and calculated as 0.125–0.25 µg/ml at stock cultures (13).

Interestingly, as discussed above, patients with Dementia had higher rates of *H.pylori* infection compared to age-matched counterparts. We found significantly lower *H.pylori* infection among patients with Dementia. It could be related to preventive ceftriaxone and pantoprazole treatment by intravenous route.

The limitation of the study is that the type of Dementia could not be determined because our patients were admitted to the hospital, especially at the advanced stage of Dementia, and the clinical data at the onset of their symptoms could not be accessed in their medical records retrospectively.

CONCLUSION

As expected and as we revealed; *Helicobacter pylori* is a curved, microaerophilic, gram-negative bacterium, thus ceftriaxone plus pantoprazole could be used in the treatment of *H.pylori* infection. Further large scale prospective studies are needed to confirm those findings.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. Ethical approval was taken from Samsun Coastal Blacksea University Hospital (GOKA/2020/4/4).

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Evaluation of micronutrients and vitamins in patients diagnosed with osteoarthritis

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ABSTRACT

Objective: Osteoarthritis (OA) is a degenerative joint disease, a leading cause of pain and disability worldwide. The hallmark of OA is pathological changes of the joint structure, such as cartilage erosion and synovial inflammation. The study aimed to evaluate the micronutrients and vitamins in patients diagnosed with osteoarthritis (OA) in Edo State, Nigeria.

Material and Methods: A total of 300 patients comprising one hundred and fifty OA subjects and 150 non-osteoarthritis subjects were recruited for this study. The levels of micronutrients (Ca, Cu, Zn, Se) were analyzed using AAS, while Vitamin D and K were measured using HPLC and spectrophotometer, respectively.

Results: The levels of copper, zinc, calcium, and vitamin K were significantly lower ($p < 0.05$) except vitamin D ($p > 0.05$) among osteoarthritis than non-osteoarthritis subjects. The selenium level was markedly higher in osteoarthritis than non-osteoarthritis subjects ($p < 0.05$). The levels of trace elements were positively correlated with vitamin D, selenium ($r = 0.23$, $p < 0.05$), calcium ($r = 0.35$, $p < 0.05$), copper ($r = 0.09$, $p > 0.05$). Blood levels of vitamin D, K, and zinc were negatively correlated with age. Vitamin D ($r = -0.01$, $p > 0.05$), vitamin K ($r = -0.02$, $p > 0.05$) and zinc ($r = -0.01$, $p > 0.05$).

Conclusion: Exposure to free radicals may be a predisposing factor to impaired synthesis of antioxidants that might be involved in the mechanical induction of osteoarthritis. Therefore, it is believed that strict metabolic control delays the development of late complications in osteoarthritis (OA). Therefore, adequate supplementation of trace elements and vitamins (D, K) in diet should be encouraged to lower the risk associated with osteoarthritis.

Keywords: Osteoarthritis, trace elements, antioxidant, disability

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INTRODUCTION

Osteoarthritis (OA) is a type of joint disease that results from the breakdown of joint cartilage and underlying bone (1). The most common symptoms are joint pains and stiffness (2). Initially, symptoms may occur only following exercise, but over time may become constant (2). Other symptoms may include joint swelling, decreased range of motion, weakness, or numbness of the arms and legs (2). The total economic burden for arthritis is estimated to be 1%–2.5% of the gross national product in Western countries. Osteoarthritis is a leading cause of disability, affecting 60 - 70% of people aged ≥ 60 years. Multiple etymologies are suspected of contributing to the formation of OA, including defective articular cartilage structure, biosynthesis, joint trauma, joint instability, inflammatory conditions, congenital and developmental abnormalities (2).

It is sometimes called a degenerative joint disease or degenerative arthritis; osteoarthritis is the most common chronic condition of the joints. The prevalence of osteoarthritis in Nigeria is estimated to be 0.4% of the population among adults aged 65 years across Africa (3). OA is found as the most prevalent arthritis in urban settings; this was found to be 55.1%, and in rural settings, all were found in South Africa ranged from 29.5%, 29.7%, up to 82.7% among adults aged 65 years (4). Other urban Hospital-based studies reporting OA of the knee are Burkina Faso, with a prevalence of 0.5% among adults. Tunisia reported a prevalence of 4.7% of knee osteoarthritis among elderly subjects and 9.9% prevalence with the musculoskeletal condition in Cameroon (5). Approximately 27 million Americans are affected by osteoarthritis. It is the most common form of arthritis, affecting about 237 million (3.3% of the population) (6). About 10% of males and 18% of females are affected (7). It is the cause of about 2% of years lived with disability. In Australia, about 1.9 million people are affected, and in the United States, 30 to 53 million people are affected (8). It becomes more common in both sexes as people become older (2). OA can affect any joint, but it occurs most often in knees, hips, lower back and neck, small joints of the fingers, and the bases of the thumb and big toe. The pain is naturally made worse by prolonged activity and relieved by rest. Stiffness is most common in the morning and typically lasts less than thirty minutes after beginning daily activities but may return after periods of inactivity. Osteoarthritis can cause a crackling noise (called "crepitus") when the affected joint moves, especially the shoulder and knee joints. A person may also complain of joint locking and joint instability. As osteoarthritis progresses, movement patterns (such as gait) are typically affected (9). Osteoarthritis is the most common cause of joint effusion of the knee (10). In smaller joints, such as the fingers, hard bony enlargements, called Heberden's nodes (on the distal interphalangeal joints) or Bouchard's nodes (on the proximal interphalangeal joints), may form, and though they are not necessarily painful, they do limit the movement of the fingers significantly. Osteoarthritis of the toes may be a factor causing the formation of bunions (10), rendering them red or swollen. In normal joints, a firm, rubbery material called cartilage covers the end of each bone. Cartilage provides a smooth, gliding surface for joint motion and cushion between the bones. The most commonly involved joints are those near the fingers' ends, at the base of the thumb, neck, lower back, knee, and hips (2). The risk factor is more significant in overweight, having one leg of a different length, and having jobs that result in high levels of joint stress (2, 7, 11). Osteoarthritis is believed to be caused by mechanical stress on the joint and low-grade inflammatory processes (12). It develops as cartilage is lost and the underlying bone becomes affected (2), as pain may make it difficult to exercise, muscle loss may occur (13, 7). Diagnosis is typically based on signs and symptoms, with medical imaging and other tests occasionally used to support or rule out other problems (2). In contrast to rheumatoid arthritis, which is primarily an inflammatory condition, in osteoarthritis, the joints do not become hot or red (2).

Damage from mechanical stress with insufficient self-repair by joints is the primary cause of osteoarthritis (14). Sources of this stress may include misalignments of bones caused by congenital or pathogenic causes; mechanical injury; excess

body weight; loss of strength in the muscles supporting a joint; and impairment of peripheral nerves, leading to sudden or uncoordinated movements (14). However, exercise, including running in the absence of injury, has not been found to increase the risk of knee osteoarthritis (15).

Several studies have shown a greater prevalence of the disease among siblings and mainly identical twins, indicating a genetic basis (16). Although a single factor is not generally sufficient to cause the disease, about half of the variations in susceptibility have been assigned to genetic factors (17).

The development of osteoarthritis is correlated with a history of previous joint injury and obesity, especially concerning knees (18). Since the correlation with obesity has been observed not only for knees but also for non-weight bearing joints and the loss of body fat is more closely related to symptom relief than the loss of body weight, it has been suggested that there may be a metabolic link to body fat as opposed to just mechanical loading (19). Changes in sex hormone levels may play a role in the development of osteoarthritis as it is more prevalent among postmenopausal women than among men of the same age (20,21). A mice study found natural female hormones to be protective while injections of the male hormone dihydrotestosterone reduced protection (22).

Increased risk of developing knee and hip osteoarthritis was found among those who work with manual handling (e.g., lifting), have physically demanding work, walk at work, and have climbing tasks at work (e.g., climb stairs or ladders) (11). In particular, with hip osteoarthritis, an increased risk of development over time was found among those who work in the bent or twisted positions (11). For knee osteoarthritis, in particular, the increased risk was found among those who work in a kneeling or squatting position, experience heavy lifting combined with a kneeling or squatting posture, and work standing up (11). Women and men have similar occupational risks for the development of osteoarthritis (11).

Osteoarthritis is a degenerative joint disease which may cause gross cartilage loss and morphological damage to other joint tissues. Basal biochemical changes occur in the earliest stages of osteoarthritis progression. The water content of healthy cartilage is finely balanced by compressive force driving water out and hydrostatic and osmotic pressure drawing water in (23). Collagen fibers exert compressive strength, whereas the Gibbs–Donnan effect and cartilage proteoglycans create osmotic pressure, which tends to draw water in (23). However, during the onset of osteoarthritis, the collagen matrix becomes more disorganized, and there is a decrease in proteoglycan content within cartilage. The breakdown of collagen fibers results in a net increase in water content (24). This increase occurs because while there is an overall loss of proteoglycans (and thus a decreased osmotic pull) (25, 26), it is outweighed by a loss of collagen (23 25). Without the protective effects of the proteoglycans, the collagen fibers of the cartilage can become susceptible to degradation and thus exacerbate the degeneration. Inflammation of the synovium (joint cavity lining) and the surrounding joint capsule can also occur, though often mild (compared to the synovial inflammation in rheumatoid arthritis).

Other structures within the joint can also be affected (27). The ligaments within the joint become thickened and fibrotic, and

the menisci can become damaged and wear away (28). Menisci can be completely absent when a person undergoes a joint replacement. New bone outgrowths, called "spurs" or osteophytes, can form on the margins of the joints, possibly in an attempt to improve the unity of the articular cartilage surfaces in the absence of the menisci. The subchondral bone volume increases and becomes less mineralized (hypomineralization) (29). These changes can cause problems functioning and subchondral bone lesions (30).

Globally, as of 2010, approximately 250 million people had osteoarthritis of the knee (3.6% of the population) (31). Hip osteoarthritis affects about 0.85% of the population (31). As of 2004, osteoarthritis globally causes moderate to severe disability in 43.4 million people (32). Together, knee and hip osteoarthritis had a ranking for disability globally of 11th among 291 disease conditions assessed (31).

As of 2012, osteoarthritis affected 52.5 million people in the United States, approximately 50% of whom were 65 years or older (8). The rate of osteoarthritis in the United States is forecast to be 78 million (26%) adults by 2040 (8).

There are ongoing efforts to determine if agents modify outcomes in osteoarthritis. Sprifermin is one candidate drug. There is also tentative evidence that strontium ranelate may decrease degeneration in osteoarthritis and improve outcomes (33).

As well as attempting to find disease-modifying agents for osteoarthritis, there is emerging evidence that a system-based approach is necessary to find the causes of osteoarthritis (34). Changes may occur before the clinical disease is evident due to abnormalities in biomechanics, biology, or structure of joints that predispose them to develop clinical disease. Thus, research focuses on defining these early pre-osteoarthritis changes using biological, mechanical, and imaging markers of osteoarthritis risk, emphasizing multi-disciplinary approaches and looking into personalized interventions that can reverse osteoarthritis risk in healthy joints before the disease becomes evident.

Guidelines outlining requirements for inclusion of soluble biomarkers in osteoarthritis clinical trials were published in 2015 (35), there are no validated biomarkers for osteoarthritis. One problem with using a specific type II collagen biomarker from the breakdown of articular cartilage is that the amount of cartilage is reduced (worn away) over time with the progression of the disease.

As a result, a patient can eventually have very advanced osteoarthritis with none of this biomarker detectable in their urine. Another problem with a systemic biomarker is that a patient can have osteoarthritis in multiple joints at different stages of disease simultaneously, so the biomarker source cannot be determined. Some other collagen breakdown products in the synovial fluid correlated with each other after acute injuries (a known cause of secondary osteoarthritis) but did not correlate with the severity of the injury (36).

Osteoarthritis occurs in people of all ages; osteoarthritis is most common in people older than 60 years of age. Common risk factors include increasing age, obesity, previous joint injury, overuse of the joint, weak thigh muscles, and genes. Metal concentrations in bones reflect long-term exposure, yet no evidence would determine whether the mobilization of

bone stores could occur so quickly that it may result in poisoning. The characteristics and long recovery time of bone tissue may reflect a chronic level of exposure and serve as a basis for an indirect assessment of environmental exposure. Among the elements necessary for life, zinc (Zn) and Copper (Cu) concentrations are often determined in highly mineralized tissues. It was found that zinc accelerates the bone formation and is essential for the correct ossification and mineralization of the skeleton, especially the femoral epiphysis. Zinc and copper are involved in the formation and metabolism of bone tissue. Naturally occurring minerals such as Calcium (Ca), Copper (Cu), selenium (Se), and zinc (Zn) have shown anti-inflammatory effects in both animal and human studies.

Animal model of OA, a deficiency of dietary Mg was established to accelerate cartilage damage (37). Copper is an essential cofactor in enzymes such as superoxide dismutase (SOD) that also needs Zn and Mn as cofactors. Many studies revealed a role for oxidative stress in the pathogenesis of OA, whereby ROS generation and impaired antioxidant status of the joint might degrade cartilage joint remodelling (38).

Selenium is also an essential cofactor for glutathione peroxidase, which may have a role in reducing the incidence of osteoarthritic lesions (39). It is unknown whether trace element status leads to disease or whether diseases are set in due to the deficiency of trace elements. However, it is generally believed that a strict metabolic control delays the development of late complications OA.

Many trace elements (micronutrients) have been recognized to play an essential role in the pathogenesis and progression of many diseases, including osteoarthritis. However, prevalence data on arthritis in Africa is very scarce despite the overwhelming report on the rising prevalence of the musculoskeletal disease. More studies are needed to address this disease's prevalence and true burden in Africa. Hence, investigating changes in the metabolism of these elements was the major reason for this research.

Recently, there has been increased interest in the incidence of osteoarthritis in elderly subjects resulting in progressive degenerative changes in the cartilage and articular tissues. Multiple etiologies are suspected of contributing to the formation of OA, including defective articular cartilage structure and biosynthesis, joint trauma, joint instability, congenital and developmental abnormalities, and inflammatory conditions. Measuring the levels of Ca, Cu, Zn, Se, and some essential vitamins necessary for Oxidative damage is essential in understanding cell dysfunction and degradation caused by oxygen free radicals in the pathobiology of degenerative joint disease.

MATERIAL and METHODS

This is a cross-sectional study of diagnosed osteoarthritis patients attending the orthopedic clinic in Central Hospital, Benin – City, Edo State, Nigeria. The study was carried out in Benin - city, an urban area, the capital of Edo state, with a population of 1147188 according to the 2006 Nigeria census. It is located at latitude 6.340 N and longitude 5.600E with 87.88m.

The Hospital serves an estimated population of 450,000 and serves as a reference center for orthopedic and treatment and

management of patients with disabilities. Participants are educated, aged between 51-90 years, dark complexion, normal, overweight, obese, married, and unmarried.

The sample size was determined according to the method of (40). The prevalence of knee osteoarthritis in Nigeria is 8.9% (41)

A random sampling method was used for the collection of three hundred samples. Blood samples comprised one hundred and fifty (150) osteoarthritis patients and one hundred and fifty (150) blood samples of non-osteoarthritis patients. The samples were collected from the blood bank of the screened patient following all legal and professional ethical documentation.

Blood samples were collected into 5ml capacity plain plastic bottles with the help of health personnel in the Hospital. All patients included were aged 51 and above with knee injury, Hip OA, non-smoker, and non-alcoholic patients. All patients excluded had Inflammatory arthritis, uncontrolled D.M., hypertension, chronic kidney disease, and uncorrected Hypo/hyperthyroidism.

Ethical clearance was obtained from Edo State Ministry of Health, Benin –City. Also, written informed consent was sort from the participants and gave assurance that the health history of the patients obtained will not be linked with the true identity of the patient when recording the outcome of my findings. The whole blood sample collected into anticoagulant and plain bottles were centrifuged using a refrigerated centrifuge at a speed of 10000 rpm for 15mins. The distinct layer was obtained, i.e., Plasma and Serum, where the plasma was kept at low temperature for vitamin D analysis. The blood serum intended for analysis was stored under a low temperature of about -20 °C.

Measurement of trace elements, vitamin k and vitamin d

The trace elements content of the digested samples (Zinc, Selenium, Copper, and Calcium) were assayed using atomic absorption spectroscopy (Buck Scientific Model VGP-210, Germany) at the University of Benin, Benin - City, Edo State, Nigeria. Their concentrations were obtained in duplicate from the absorbance read.

Vitamin K and Vitamin D were analyzed using Spectrophotometer and HPLC (C18), respectively.

Statistical analysis: All data obtained were analyzed using SPSS Version 23.0. The comparison between the osteoarthritis and non- osteoarthritis subjects was performed using the student's unpaired t-test, correlation, and chi-square. The statistical significance was beset at $p < 0.05$.

RESULTS

The socio-demographic variables of the three hundred (300) subjects in the study revealed that 19.3% were between the ages of 51-60years, 57.3% were between 61-70years, 7.3% were between 71-80years and 16.0% were between 81-90 years. Of the total subjects, 39.6% were males, and 60.3% were females. In addition, 52.6% were singles, and 47.3% were married (Table1). Of the total subjects, 33.3% had a primary level of education, 50.0% had a secondary level of education, and 16.6% had a tertiary level of education. In addition, 1.0% were underweight (BMI of 16.5 kg/m²), 66.6% were normal (BMI of 23.6kg/m²), 30.0% were overweight (BMI of 28.6 kg/m² and 2.3% were obese (BMI of 33.5 kg/m²). Of the total subjects, 20.0% were Bini, 13.3% Ibos and 66.6% Yoruba (Table 2)

Table 3 shows the blood calcium levels, trace elements, vitamin K, and D of osteoarthritis patients and the control group. It was observed that the level calcium, trace elements (Copper, zinc, and selenium), vitamin K were statistically significant ($p < 0.05$) in osteoarthritic patients when compared with the control group.

Table 4 shows a post-hoc (Bonferroni) multiple comparisons of calcium and copper. It was observed that calcium levels in female osteoarthritic subjects were statistically significantly higher than in female control ($p < 0.05$), while copper was non-significant across the group.

Table 5 shows a post –hoc (Bonferroni) multiple comparisons of zinc and selenium. It was observed that the level of selenium in male osteoarthritic subjects was statistically significantly higher than the female and male control group ($p < 0.05$), while zinc was higher in the female control group than male subjects ($p < 0.05$).

Table 6 shows a post –hoc (Bonferroni) multiple comparisons of vitamin D and K. It was observed that levels of vitamin D in female osteoarthritic subjects were statistically significantly higher than male osteoarthritic subjects ($p < 0.05$) while vitamin K was non-significant across the group.

Table 7 shows correlation of vitamin D, K, age, calcium and trace elements. It was observed that there was positive significant relationship between vitamin D, calcium($r = 0.35, p < 0.05$), selenium($r = 0.22, p < 0.05$), vitamin K ($r = 0.48, p < 0.05$) except zinc ($r = -0.19, p > 0.05$) which was negatively correlated. In addition, age was negatively correlated with vitamin D ($r = -0.01, p > 0.05$), vitamin K($r = -0.02, p > 0.05$), zinc($r = -0.01, p > 0.05$) except calcium($r = 0.04, p > 0.05$) that was non- significant positively correlated.

Table 1: Distribution of demographic factors of osteoarthritis

Demographic factors	Total (n=300)	Osteoarthritis (n=150)	Control (n=150)	X ²	p-value
Age (years)					
51-60	58(19.3%)	30(20%)	28(18.6%)	176.48	<0.05
61-70	172(57.3%)	84(56%)	88(58.6%)		
71-80	22(7.3%)	8(5.3%)	14(9.3%)		
81-90	48(16%)	28(18.6%)	20(13.3%)		
Sex					
Male	119(39.6%)	59(39.3%)	60(40.0%)	12.81	<0.05
Female	181(60.3%)	91(60.6%)	90(60.0%)		
Marital status					
Single	158(52.6%)	50(33.3%)	108(72%)	2.18	P=0.140
Married	142(47.3%)	100(66.3%)	42(28%)		

Table 2: Distribution of demographic factors of osteoarthritis

Demographic factors	Total (n=300)	Osteoarthritis (n=150)	Control N=150	X ²	p-value
Educational status					
Primary	100(33.3%)	80(53.3%)	20(13.3%)	62.07	<0.05
Secondary	150(50.0%)	60(40.0%)	90(60.0%)		
Tertiary	50(16.6%)	10(6.6%)	40(26.6%)		
Body mass index (kg/m ²)					
Underweight	3(1.0%)	3(2.0%)	0(0.0%)	45.53	<0.05
Normal	200(66.6%)	100(66.6%)	100(66.6%)		
Overweight	90(30.0%)	45(30.0%)	45(30.0%)		
Obese	7(2.3%)	2(1.33%)	5(3.3%)		
Ethnicity					
Bini	60(20.0%)	30(20.0%)	30(20.0%)	275.78	<0.05
Igbo	40(13.3%)	10(6.6%)	30(20.0%)		
Yoruba	200(66.6%)	110(73.3%)	90(60.0%)		

Values in parenthesis are percentages.

Table 3: Level of calcium, trace elements, vitamin d and k among osteoarthritis and non osteoarthritis patients

Variable	Osteoarthritis (n=150)	Control (n= 150)	p-value
Calcium (mmol/L)	1.56 ± 0.01	1.96 ± 0.02	<0.05**
Copper (mmol/L)	8.68 ± 0.30	9.84 ± 0.35	<0.05**
Zinc (µm/L)	12.71 ± 0.15	13.61 ± 0.19	<0.05**
Selenium (ng/mL)	141.13 ± 4.39	106.07 ± 3.01	<0.05**
Vitamin K (mm/L)	1.59 ± 0.02	1.67 ± 0.02	<0.05**
Vitamin D (ng/L)	50.59 ± 1.28	51.75 ± 1.31	>0.05*

Table 4: Multiple comparison of calcium and copper among sex

Bonferroni					
Dependent Variable	(I) SEX	(J) SEX	Mean Difference (I-J)	Std. Error	P-value.
CALCIUM(mmol/l)	male subjects	female subject	-.06	.04	1.000
		male control	.06	.05	1.000
		female control	.08	.04	.452
	female subject	male subjects	.06	.04	1.000
		male control	.12	.04	.052
		female control	.14*	.04	.004
	male control	male subjects	-.06	.05	1.000
		female subject	-.12	.04	.052
		female control	.02	.04	1.000
	female control	male subjects	-.08	.04	.452
		female subject	-.14*	.04	.004
		male control	-.02	.04	1.000
COPPER(umol/l)	male subjects	female subject	.70	.68	1.000
		male control	-.83	.75	1.000
		female control	-.65	.68	1.000
	female subject	male subjects	-.70	.68	1.000
		male control	-1.54	.67	.145
		female control	-1.35	.61	.156
	male control	male subjects	.83	.75	1.000
		female subject	1.54	.68	.145
		female control	.18	.67	1.000
	female control	male subjects	.65	.68	1.000
		female subject	1.35	.61	.156
		male control	-.18	.68	1.000

*The mean difference is significant at the 0.05 level.

Table 5: Multiple comparison of Zinc and Selenium among sex

Bonferroni					
Dependent Variable	(I) SEX	(J) SEX	Mean Difference (I-J)	Std. Error	P-value
ZINC (umol/l)	male subjects	female subject	-.24	.36	1.000
		male control	-1.01	.39	.066
		female control	-1.08*	.36	.019
	female subject	male subjects	.24	.36	1.000
		male control	-.77	.35	.193
		female control	-.84	.32	.057
	male control	male subjects	1.01	.39	.066
		female subject	.77	.36	.193
		female control	-.07	.36	1.000
	female control	male subjects	1.08*	.36	.019
		female subject	.84	.32	.057
		male control	.07	.36	1.000
SELENIUM (ng/ml)	male subjects	female subject	3.99	7.74	1.000
		male control	36.06*	8.49	.000
		female control	38.45*	7.76	.000
	female subject	male subjects	-3.99	7.74	1.000
		male control	32.06*	7.70	.000
		female control	34.45*	6.88	.000
	male control	male subjects	-36.06*	8.49	.000
		female subject	-32.06*	7.70	.000
		female control	2.38	7.71	1.000
	female control	male subjects	-38.44*	7.6	.000
		female subject	-34.45*	6.88	.000
		male control	-2.39	7.71	1.000

*. The mean difference is significant at the 0.05 level.

Table 6: Multiple comparison of vitamin D and K among sex

Dependent Variable	(I) SEX	(J) SEX	Mean Difference (I-J)	Std. Error	P-value
VITAMIN K(mmol/l)	male subjects	female subject	-.02	.048	1.000
		male control	-.08	.052	.828
		female control	-.09	.05	.356
	female subject	male subjects	.02	.05	1.000
		male control	-.06	.05	1.000
		female control	-.07	.04	.498
	male control	male subjects	.08	.05	.828
		female subject	.06	.04	1.000
		female control	-.01	.05	1.000
	female control	male subjects	.09	.05	.356
		female subject	.07	.04	.498
		male control	.01	.05	1.000
VITAMIN D(ng/L)	male subjects	female subject	-9.78*	2.61	.001
		male control	-5.03	2.85	.474
		female control	-5.12	2.61	.306
	female subject	male subjects	9.78*	2.61	.001
		male control	4.73	2.59	.412
		female control	4.66	2.32	.271
	male control	male subjects	5.04	2.89	.474
		female subject	-4.74	2.59	.412
		female control	-.08	2.59	1.000
	female control	male subjects	5.12	2.61	.306
		female subject	-4.66	2.31	.271
		male control	.08	2.59	1.000

Table 7: Correlation of age with trace elements and vitamin D and K

PARAMETERS	R- VALUE	P-VALUE
AGE/VITAMIN D	-0.01	P>0.05
AGE/ VITAMIN K	-0.02	p>0.05
AGE/ZINC	-0.01	p>0.05
AGE/SELENIUM	0.04	P>0.05
AGE/COPPER	0.02	p>0.05
AGE/CALCIUM	0.04	p>0.05
VITAMIN D/ ZINC	-0.19	P<0.05

p<0.05(significant) , p>0.05(non-significant)

DISCUSSION

Osteoarthritis is a chronic progressive degenerative disorder of synovial joints affecting the articular cartilage and the underlying subchondral bone (42). The cause of OA is multifactorial, including genetic, endocrine, function and exercise, and nutritional consideration (43, 44). Bone formation and metabolism are also modulated by trace elements (zinc, copper, and selenium), vitamin D, and K, in addition, calcium and phosphorus. Trace elements are essential for bone growth and development because the components interact with the bone matrix and affect bone metabolism (45). These minerals are also implicated in the pathology, diagnosis, and treatment of osteo-disorder like OA (46). To further clarify the relationship between trace elements and effect on bone matrix density in OA, we measured serum levels of zinc, copper, selenium, vitamin D, and K in OA and analyzed their correlation with bone matrix density. Few studies have concentrated their efforts on the functional status and periodic measurement of some trace elements that help in the lubrication of vital joints ensuring holistic care and maintenance of the elderly subjects. This research was aimed at establishing the effect of antioxidant and vitamin (D and K) on bone mineralization by evaluating the level of calcium, trace elements (Copper, selenium, and zinc), and vitamin (D and K) in osteoarthritic subjects. A total of three hundred (300) subjects were recruited in this study; one hundred fifty (150) diagnosed osteoarthritic subjects and (150) healthy non-osteoarthritic subjects within the age of 51-90 years in Edo state.

In this study, it was observed that there was a significant difference across the age ($p<0.05$), which suggest that osteoarthritis is independent of age, but as age increase, there is a tendency of bone demineralization resulting in osteoarthritis. It was observed that 60.6% of females had osteoarthritis, which agrees with previous work carried out by (47), which stated that a higher prevalence of physical disability for the basal activity of daily living was more common in women than men.

In this study, it was observed that the levels of calcium, copper, zinc, vitamins K and D were low in osteoarthritis compared with the control group ($p<0.05$) except vitamin D, which was not statistically significant ($P>0.05$). It was also observed that selenium level was higher in OA than in the control group ($p<0.05$). The significantly lower calcium, copper, zinc, vitamin K, and D levels could be attributed to endothelial injury, resulting from oxidative damage of the amino acid needed for tissue lubrication, repair, cell signal, and growth (48). Biochemically, reduced serum levels of trace elements might expose the individual to damages mediated through oxidative stress.

Oxidative stress and the cellular antioxidant defence system are regulated in a coordinated fashion during inflammation. It is known that reactive oxygen species (ROS) such as hydrogen peroxide and superoxides are released and scavenged during wound healing. Glutathione is another prominent player in the cellular antioxidant function (48). Increasing glutathione suppresses Hepatic stellate cells (HSCs) growth and activation (48). It also stimulates TGF- β and suppresses glutamate-cysteine ligase (GCL), the rate-limiting enzyme in glutathione biosynthesis (48).

In this study, it was observed that the level of copper and zinc was lower ($p<0.05$). Zinc is an activator of numerous metal enzymes that can stimulate bone metabolic enzymes such as alkaline phosphatases, collagenase, and sulfuricolyases. Zinc also influence 1,25 -OH vitamin D3 and calcitonin concentration (49,50). It can stimulate gene expression of transcription factors such as runt-related transcription factor 2, which is related to differentiation forming osteoblastic cells; zinc can inhibit osteoclastic bone resorption by inhibiting osteoclastic-like cells formation from bone marrow cells by stimulating apoptotic cells death of mature osteoclasts (51). Bone growth retardation is common in various conditions associated with dietary zinc deficiency, suggesting that zinc compound may be a novel supplement factor in preventing and treating osteo-disorder like OA (51). The low level of zinc found in this study could be attributed to the role of oxidative stress in the pathogenesis of OA due to ROS generation and impaired antioxidant status of the joint resulting in the degradation of cartilage joint remodelling (38). Arikan et al. (52) found that zinc is positively correlated with the bone matrix density of the lumbar vertebrates, but different was found in this study ($r = -0.19$, $p<0.05$), which indicate dietary zinc deficiency and malabsorption was sufficient in OA. Roughly 2 - 4grams of zinc (53) are distributed throughout the human body, mainly the brain, muscles, bones, kidney, and liver, with the highest concentrations in the prostate and parts of the eye (54). Zinc homeostasis also plays a critical role in the functional regulation of the central nervous system (55,56). Dysregulation of zinc homeostasis in the central nervous system results in excessive synaptic zinc concentrations and is believed to induce neurotoxicity resulting in mitochondrial oxidative stress (e.g., by disrupting certain enzymes involved in the electron transport chain, including complex I, complex III, and α -ketoglutarate dehydrogenase), the dysregulation of calcium homeostasis, glutamatergic neuronal excitotoxicity, and interference with intraneuronal signal transduction (57,55).

Zinc deficiency is usually due to reduced or insufficient dietary intake. Still, it can be associated with malabsorption, acrodermatitis enteropathica, chronic liver disease, chronic renal disease, sickle cell disease, diabetes, malignancy, and other chronic illnesses such as osteoarthritis, especially in the elderly (58). In this study, the copper level was low in OA compared with the control group ($p < 0.05$), which could be attributed to oxidative stress from reactive oxygen species (ROS); but contrast in other studies that found increased in blood serum Cu concentration, was even considered to be a marker of clinical activity of this disease (59).

Copper plays an important role in metabolism in the nervous system, hematogenesis, skeleton construction, connective tissue, and cross-linkage of elastin and collagen protein; thus, copper is implicated in bone development and repair (60). Rodriguez et al. (61) conclude that copper stimulates MSC differentiation preferentially toward the osteogenic lineage. Copper deficiency may influence the synthesis and the stability of bone collagen and may induce skeleton development disorder resulting in osteo- disorder like OA copper supplement may be a potential strategy to treat and prevent involutional osteo- disorder (62).

In this study, the level of selenium was higher in OA patients than in control ($p < 0.05$) which could be attributed to the mild severity and duration of the disease whose mechanism is to alleviate the pain generated due to reactive oxygen species (ROS) from oxidative stress, but the contrast in other studies which state that decreased levels of selenium and the activity of selenium-dependent enzymes have also been studied in other diseases, including epilepsy, which showed a strong correlation between their reduction and severity of the disease (63). Selenium is also an essential cofactor for glutathione peroxidase, which may reduce the incidence of osteoarthritic lesions (39); in addition to a strong association of disease duration and severity with serum concentrations of Se. However, selenium is an essential constituent of the glutathione peroxidase enzyme. Its deficiency results in a marked decline in glutathione peroxidase activity of many tissues, leading to increased oxidative stress. In humans, decreased serum Se levels are unlikely to happen, but maybe the etiological factor of some severe disorders such as Keshan disease (endemic cardiomyopathy) and Kashin-Beck disease (endemic osteoarthritis).

In this study, the level of vitamin K was lower in OA compared with the control group ($p < 0.05$), which reflects the severity of the disease and oxidative damage (51). Increased supplement of vitamin K will prevent the progression of OA and lower the risk associated with OA. Vitamin K is a cofactor of gamma-glutamyl carboxylase, which plays an important role in the activation of gamma- glutamate (gla) containing protein that negatively regulates calcification. This vitamin deficiency status might be associated with OA, in which cartilage calcification plays a role in the pathogenesis of the disease. Much evidence had agreed that a sufficient level of vitamin K is associated with a lower risk of OA and pathological joint features. Despite a plausible biological rationale and a positive observational study, many findings do not support a significant effect of vitamin K supplementation on osteoarthritis for all persons. Of note, despite previous studies demonstrating an association between poor vitamin K

status and bone health (64), the parent trial did not demonstrate a significant effect of vitamin K supplementation on bone mineral density in the hip or spine (65).

In this study, the level of vitamin D was not significant in OA compared with the control group ($p > 0.05$); the reason for this was unclear, which will be elucidated in further study. Vitamin D has a significant role in calcium homeostasis and metabolism. Its discovery was due to an effort to find the dietary substance lacking in children with rickets (the childhood form of osteomalacia) (66). However, vitamin D deficiency has become a global problem in the elderly and remains common in children and adults (67,68). Low blood calcifediol (25-hydroxy-vitamin D) can result from avoiding the sun (69). Deficiency results in impaired bone mineralization and bone damage, leads to bone-softening diseases (70), including rickets, osteomalacia, and osteoarthritis. Vitamin D supplementation in the general population is inconsistent (71,72). The effect of vitamin D supplementation on mortality is not clear, with one meta-analysis finding a small decrease in mortality in elderly people (73) and another concluding no clear justification exists for recommending supplementation for preventing many diseases, and that further research of similar design is not needed in these areas (74).

For older people with osteoporosis, taking vitamin D with calcium may help prevent hip fractures, but it also slightly increases the risk of stomach and kidney problems (75). Supplementation with higher doses of vitamin D in those older persons than 65 years may decrease fracture risk (76). The effect may be smaller for people living independently than in institutions (77). It helps in regulating calcium in the human body (78). The active vitamin D metabolite calcitriol mediates its biological effects by binding to the vitamin D receptor (VDR), principally located in the nuclei of target cells. The binding of calcitriol to the VDR allows the VDR to act as a transcription factor that modulates the gene expression of transport proteins (such as TRPV6 and calbindin), which are involved in calcium absorption in the intestine (79). The vitamin D receptor belongs to the nuclear receptor superfamily of steroid/thyroid hormone receptors, and VDRs are expressed by cells in most organs, including the brain, heart, skin, gonads, prostate, and breast.

VDR activation in the intestine, bone, kidney and parathyroid gland cells leads to the maintenance of calcium and phosphorus levels in the blood (with the assistance of parathyroid hormone and calcitonin) and to the maintenance of bone content (80). One of the most important roles of vitamin D is to maintain skeletal calcium balance by promoting calcium absorption in the intestines, promoting bone resorption by increasing osteoclast number, maintaining calcium and phosphate levels for bone formation, and allowing proper functioning of parathyroid hormone to maintain serum calcium levels. Vitamin D deficiency can result in lower bone mineral density and an increased risk of reduced bone density (osteoporosis) or bone fracture because a lack of vitamin D alters mineral metabolism in the body.

The VDR may be involved in cell proliferation and differentiation. Vitamin D also affects the immune system, and VDRs are expressed in several white blood cells, including monocytes and activated T and B cells (81). Apart from VDR activation, various alternative mechanisms of

action are under study, such as inhibition of signal transduction by hedgehog, a hormone involved in morphogenesis (82).

In this study, it was observed that age was negatively correlated with vitamin D, K, and zinc ($p > 0.05$) which could be attributed to a decrease in trace elements with increasing age, which is in agreement with the previous study (83) which state that decreases trace elements (Copper, zinc), vitamin K and bone matrix density decrease with age therefore, we believe enriching the diet with trace elements should be considered in the elderly population. Although, Oxidative damage to essential cell components caused by oxygen free radicals results in the pathobiology of degenerative joint disease (84). It is generally believed that a strict metabolic control delays late complications in OA.

CONCLUSION

Osteoarthritis is a degenerative joint disease with an age-associated increase in incidence and prevalence. The hallmark of OA is the pathological changes of the joint structure, such as cartilage erosion and synovial fluid inflammation. Thus far, no efficient treatment can alter the progression of OA except the non-pharmacological prevention through lifestyle and nutrition. It is good to know that some trace elements like zinc, selenium, copper, and calcium are conducive to the prevention and treatment of OA. To some extent, the status of trace elements depends on the external environment (nutrition) and internal factors (individual absorption and metabolism of trace elements, genetic tendency, age, and gender). However, knowledge in this area is much needed to elucidate the effect of trace elements on OA. The protective effect has been found. However, theoretical and practical issues on supplementation in the prevention and treatment of OA are still unknown. Despite the efficacy of trace elements, the impact factor is still limited due to the obtainment of these elements in combination. Further studies are needed to confirm the dosage, concentration, and interaction of individual trace elements on OA, thereby preventing and treating OA. This study shows that OA subjects have significantly lower levels of copper, calcium, zinc, vitamin D, vitamin K, and elevated selenium levels than control subjects. The low level of trace elements in OA resulted from oxidative stress generated from reactive oxygen species (ROS) and an increase in age. This result showed that OA subjects were prone to oxidant stress, which led to altered antioxidant levels.

Exposure to free radicals may predispose to impaired synthesis of antioxidants. Therefore, it is believed that strict metabolic control delays the development of late complications in osteoarthritis (OA). Therefore, adequate supplementation of trace elements and vitamins (D, K) in diet should be encouraged to lower the risk associated with osteoarthritis.

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Reliability of laparoscopic lateral suspension videos on YouTube platform

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ABSTRACT

Objective: YouTube is one of the most popular websites globally and its content is not limited to entertainment. The aim of this study is to evaluate the reliability, quality and quantity of information and surgical steps in YouTube videos about laparoscopic lateral suspension with mesh for the surgical treatment of pelvic organ prolapse (LLS).

Material and Methods: A search on YouTube was performed with the key words; "laparoscopic lateral suspension", "lateral suspension", "pelvic organ prolapse surgery", "POPS with mesh", "Pelvic Organ Prolapse Suspension". Each video was further analysed in terms of reliability, quality and quantity of information.

Results: A total of 44 videos were evaluated after excluding 36 of the 88 videos associated with LLS. According to the usefulness score, the videos were divided into two groups. 61.4% (n=27) of the videos were in GroupI (not useful and slightly useful) and 38.6% (n=17) were in GroupII (useful and very useful). There was no difference between the groups in terms of video length, number of views, number of likes, number of dislikes, number of comments and number of subscribers. A Spearman's rank correlation analysis found no correlation between the usefulness score and like ratio, views ratio, like / view rate, like/subscriber rate, view/subscriber rate, VPI rates.

Conclusion: Since the videos uploaded to YouTube do not pass a preliminary examination, their reliability is low even if they are uploaded by health professionals. There is no relationship between quantitative information of the LLS videos and the usefulness scores of the videos.

Keywords: Laparoscopic Lateral Suspension (LLS), Quality Information, Quantitative Information YouTube

INTRODUCTION

Theoretical and visual education in the medical field, especially in surgical branches, came from the master-apprentice relationship, academic journals, textbooks, articles describing clinical experience, review articles, meta-analyses and case presentations (1). The Internet has begun to change and overcome previous education restrictions with sharing information globally regardless of time zone (2, 3).

The recent growth of social media platforms has greatly increased surgeons' access to visual learning and monitoring of operations they've never done before (1).

One of the most widespread Internet-based visual information and entertainment platforms, YouTube (www.youtube.com) has more than 2 billion video views every day (4). Surgical practice videos related to many specialties and procedures are shared on this platform. YouTube has become an important source of visual information for medical students, residents, and even surgical professionals (1).

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For the first time, Keelan et al. (5) reported on the quality of YouTube videos regarding immunization in 2007 and later, many researchers have conducted research on the reliability of YouTube videos such as endometrioma cystectomy, prostate cancer, bariatric surgery, tonsillectomy, vaginismus and hysterectomy (1, 6-10). Although these studies have analysed the accuracy of YouTube videos, debates continue regarding the reliability of these videos due to the diversity of sources and lack of peer-reviews (7, 11, 12). In our study, we aimed to review the videos that give information about the treatment of pelvic organ prolapse laparoscopically by using Lateral Polypropylene Mesh (Laparoscopic lateral suspension with mesh (LLS)).

MATERIAL and METHODS

An observational study was planned on 21 March 2021. A search on YouTube was performed with the key words; "laparoscopic lateral suspension", "lateral suspension", "Pelvic Organ Prolapse Suspension surgery", "POPS with mesh", "Pelvic Organ Prolapse Suspension" and "Pelvic Organ Prolapse Surgery (POPS) with Lateral Mesh". Top 50 videos were included using each keyword.

Being in a language other than English, presentations without audio or written information, and duplicated videos were excluded from the study. The videos were ranked by relevance according to the current YouTube default, and two researchers (E.E., E.E.D.) with experience in LLS surgery evaluated the videos.

The source of the videos was recorded as Doctors or Practitioners (D/P), Hospitals or Clinics (H/C), Medical Website or TV Channel (M/T), and Commercial Website or Civilians (C/I).

Compiled YouTube video data: the number of days since the upload date of the videos, the length and number of views of the videos, likes, dislikes, comments and subscribers were recorded. Quantitative information of the videos was obtained as like/ view, like/subscriber, view/subscriber, like ratio (like *100/ [like + dislike]), view ratio (number of views/days), and Video Power Index (VPI; like ratio * view ratio/100) were calculated (13).

The reliability of the videos was evaluated with a predefined "health videos usefulness score" that evaluates the presentation of information on causes, symptoms, diagnosis, treatment and recovery for a particular health issue (14). The variables were scored as follows: 0, not mentioned; 1, mentioned briefly; and 2, described in details. The evaluation was according to not useful (0), slightly useful (1–3), useful (3–7) and very useful (7–10) in total scoring (**Table-1**). All videos were divided into two groups; not useful and slightly useful (Group I), useful and very useful (Group II).

Table1. Usefulness score criteria

Score criteria
Cause
Symptoms
Diagnosis
Treatment
Recovery

Surgical analysis

Videos describing the same surgical steps were followed (15, 16). First step; endoscopically creating anterior dissection of the vesicovaginal space to the lowest possible point. Second step; insertion of a T or V-shaped mesh consisting of a central rectangle (approximately 4 - 6 cm) and two long side arms (approximately 2*18 cm) in the abdomen. Third step; fixation of the mesh from the center to the dissected area with taker and/or suture. Fourth step; creating a retroperitoneal canal by making a 3 mm skin incision 2 cm above the iliac crest and 4 cm behind the anterior superior iliac spine on both sides. Fifth step; pulling the mesh arms from the retroperitoneal canal created and releasing them to provide tension with retroperitoneal fibrosis.

Statistical analysis

Statistical analysis was performed using SPSS Version 20 (SPSS, Inc., Chicago, IL). Continuous variables were given as mean \pm standard deviation, while categorical ones were given as number and percentage (%). The kappa coefficient was used to evaluate the agreement between two independent reviewers. The normality was tested with the Shapiro-Wilk Test. The Mann-Whitney U test was used for comparison of ordinal variables or continuous variables that did not fit a normal distribution. The independent t- test was used to compare continuous variables with normal distributions. The Pearson Chi-Square and Fisher's Exact Test were used to analysing the crosstabs. In all analyses, $p < 0.05$ was taken to indicate statistical significance.

RESULTS

A total of 44 videos on lateral suspension were evaluated. Sixty-one percent (61.4%, $n=27$) of the videos were Group I (not useful and slightly useful), thirty-eight percent (38.6%, $n=17$) were Group II (useful or very useful).

Total video analysis and features are summarized in **Table-2**. The mean numbers (mean \pm SD (min-max)) of video length(sec.), number of views, likes, dislikes, comments and subscribers were 632.8 ± 569.9 (77-3035), 1790.8 ± 3749.2 (16-22849), 10.9 ± 9.5 (0-33), 1.0 ± 2.2 (0-9), 1.0 ± 2.2 (0-9), 5839.3 ± 23549.3 (5- 153000) respectively.

Video content and usefulness criteria for LLS are summarized in **Table 3**. A statistical difference was observed between groups in terms of cause, symptoms, diagnosis, treatment, and recovery, which constitute the usefulness criteria ($p=0.001$, $p=0.041$, $p=0.001$, $p=0.047$, $p=0.001$, respectively). Only one of the videos was performed as robotic surgery. There was no statistical difference in terms of skin incision site on the abdomen ($p=0.052$). As the mesh material used, polyethylene (mesitylene) was used in only one of the videos.

The method used more frequently in Group I than Group II in the fixation of the mesh material was saturation (66.7%, 35.3%), and a statistical difference was observed between the groups ($p=0.042$). The most commonly used fixation method in Group II was taker (41.2%). However, no difference was observed between the groups ($p=0.103$).

A Spearman's rank correlation analysis found no correlation between the usefulness score and like ratio, views ratio, like / view, like/subscriber rate, view/subscriber, VPI rates (Table4).

There was a negative correlation between the length of the videos and the view /subscriber ratio ($r = -0.433$, $p = 0.003$). Negative correlation was observed between day of the upload and like ratio ($r = -0.310$, $p = 0.041$), like/ view ($r = -0.648$, $p = 0.001$) of the videos.

Table 2. Video analysis of the Laparoscopic Lateral Suspension in regards

	GroupI (n=27)	GroupII (n=17)	Total (n=44)	P value
Videos	61.4 %	38.6 %	100 %	
Source				
Surgeon/practitioner (S/P)	25 (92.6%)	16 (94.1%)	41 (93.2%)	0.159
Hospital/free clinic (H/C)	2 (7.4%)	1 (5.9%)	3 (6.8%)	
Medical website/ TV canal (M/T)				
Commercial websites/civilians (C/I)				
Time passed since video upload (days)	1311.7 \pm 1159.5 (180-5110)	1090.2 \pm 870.6 (90-2555)	1226.2 \pm 1052 (90-5110)	0.514
Video length (sec.)	695.9 \pm 604 (77-3035)	532.6 \pm 511.7 (197-2400)	632.8 \pm 569.9 (77-3035)	0.158
Number of views	1945.8 \pm 4597.9 (16-22849)	1544.6 \pm 1821.2 (32-6197)	1790.8 \pm 3749.2 (16-22849)	0.691
Number of likes	9.8 \pm 9 (0-33)	12.7 \pm 9.1 (0-30)	10.9 \pm 9.5 (0-33)	0.205
Number of dislikes	1.2 \pm 2.6 (0-9)	0.7 \pm 1.14 (0-3)	1.0 \pm 2.2 (0-9)	0.634
Number of comments	1.4 \pm 2.6 (0-9)	0.4 \pm 0.87 (0-3)	1.0 \pm 2.2 (0-9)	0.470
Number of subscribers	7004 \pm 29245.1 (5- 153000)	3988.2 \pm 9731.6 (11-35500)	5839.3 \pm 23549.3 (5- 153000)	0.781
Like ratio	94.4 \pm 12.6 (50-100)	96.1 \pm 5.0 (84-100)	95.1 \pm 10.3 (50-100)	0.420
Views ratio	1.19 \pm 1.81 (0.4 - 8.9)	1.19 \pm 0.88 (0.5- 3.4)	1.19 \pm 1.51 (0.4 - 8.9)	0.201
Like/view	0.02 \pm 0.02 (0-0.07)	0.02 \pm 0.03 (0-0.12)	0.021 \pm 0.025 (0- 0.12)	0.595
Like/subscriber	0.17 \pm 0.52 (0-2.6)	0.2 \pm 0.4 (0- 1.2)	0.18 \pm 0.47 (0-2.6)	0.562
View/ subscriber	88.5 \pm 400 (0-2077.1)	24.9 \pm 79.2 (0-329.5)	64 \pm 316.4 (50-100)	0.727
VPI (Video Power Index)	1.0 \pm 1.4 (0-7.4)	1.2 \pm 0.7 (0.3- 3)	1.1 \pm 1.2 (0-7.4)	0.099
Total score	1.44 \pm 0.69 (0-3)	5.4 \pm 0.7 (4-10)	2.9 \pm 1.19 (0-10)	< 0.001*

*Statistical significance was defined as $p < 0.05$. NS: Not Significant ($p > 0.05$).

Table 3. Surgical step of the LLS in regards to usefulness criteria.

		GroupI (n=27)	GroupII (n=17)	P value
Usefulness scores	Cause / indication	1 (0-2) 15 (55.6%)	2 (0-2) 17 (100%)	0.001*
	Symptoms/ Surgical Option	1 (0-2) 3 (85.2%)	2 (0-2) 17 (100%)	0.041*
	Diagnose /Benefit	1 (0-2) (2.3%)	2 (0-2) 16 (94.1%)	< 0.001*
	Treatment /Postoperative Life	0	1 (0-2) 2 (11.8%)	0.047*
	Recovery / Complication	0	1 (0-2) 5 (29.4%)	0.001*
Type of surgery	Laparoscopic	26 (96.3%)	17 (100%)	0.319
	Robotic	1 (3.7%)	0	
Vesicovaginal dissection	Yes	27 (100%)	17 (100%)	NS
	No	0	0	
Prepared Mesh	Polypropylene	27 (100%)	16 (94.1%)	0.162
	Polyethylene (Mersilene)	0	1 (5.9%)	
Mesh fixation	Suture	18 (66.7%)	6 (35.3%)	0.042*
	Taker	5 (18.5%)	7 (41.2%)	0.103
	Both	4 (14.8%)	2 (11.8%)	0.772
	Non-information	0	1 (5.9%)	0.162
Skin incision	Yes	2 (4.5%)	5 (29.4%)	0.054
	Non -information	25 (92.6)	12 (70.6%)	
Mesh arm station	Free	27 (100%)	15 (88.2%)	0.144
	Fix	0	2 (11.8%)	
Indication	Cuff Prolapse	13 (29.5%)	9 (52.9%)	NS
	Hysteropexy	1 (3.7%)	1 (5.9%)	
	Hysteropexy +cystocele	12 (44.4%)	7 (41.2%)	
	Cystocele	1 (3.7%)	0	

*Statistical significance was defined as $p < 0.05$. NS: Not Significant ($p > 0.05$).

Table 4. Spearman correlation analysis between the usefulness score and video interest rates of viewers.*Statistical significance was defined as $p < 0.05$.

Useful score	views		Views		Like/view		Like/subscriber		View/ subscriber		VPI	
	<i>p</i>	<i>p</i>	<i>rho</i>	<i>p</i>	<i>rho</i>	<i>p</i>	<i>rho</i>	<i>p</i>	<i>rho</i>	<i>p</i>	<i>rho</i>	<i>p</i>
Useful Score	1	0.047	0.764	-0.082	0.597	0.288	0.151	0.329	0.160	0.299	0.091	0.558
Length	-0.224	0.131	0.395	0.033	0.832	0.939	0.233	0.187	-0.208	0.176	-0.433	0.003*
Day Upload	-0.091	0.556	0.001*	-0.310	0.041*	0.233	-0.648	0.001*	-0.197	0.200	0.176	0.256
											0.113	0.466

DISCUSSION

The source of the videos uploaded on YouTube is important. Most of the videos uploaded about bariatric surgery were evaluated by Erdem et al, D/P (39%) and M/T (45%); most of the videos uploaded about endometriosis surgery were evaluated by Kaya et al, D/P (82%) and H/C (11%) and they evaluated the sources of helpful and unhelpful videos alike (1, 7). Lee et al reported that most of the videos about gallstone disease were uploaded by M/T (23%) and C/I (48.9%), but helpful videos were uploaded by D/P and MT (14). Accordingly, Erdem et al. reported that the total videos they evaluated (78.3%), and Frongia et al reported that the total videos (71.8%) they evaluated as useful or very useful, and they both argued that this was because most of the video sources were uploaded to D/P (1,17).

In many studies, it has been reported that the videos uploaded by health professionals are important, but the rate of usefulness of uploaded videos to be considered useful is low.

It has been shown that 29% of the videos about anorexia (18), 37.95% of the videos about breast self-examination (19), 24% of the videos about inflammatory bowel disease (20), 30.7% of the videos about lingual orthodontic treatment (21), 30% of the videos about rheumatoid arthritis (22) and 25% of the videos about vaginismus were evaluated as useful (9).

Another study looking at laparoscopic cholecystectomy showed that the highest-ranked videos after a search on YouTube showed the optimal surgical technique, but half of the videos exhibited unsafe maneuvers and only 10% were reliable videos (23). A study, rating 32 videos demonstrating the surgical technique of urethral sling procedures found that none of the videos showed a complete list of predetermined surgical steps (24). In another study with endometriosis surgery, videos were shown to be only 20% useful or very useful (7). Our study was generally compatible with other studies, the source of the total videos was D/P and 38.6% of them were observed as useful or very useful.

Sood et al. regarding kidney stones (26) and Sahin et al. regarding retinitis pigmentosa (25) reported that videos which were useful or very useful were viewed significantly higher than 'not useful or slightly useful' videos. Butler et al. found a weak correlation between the usefulness score and the number of video views (28). On the contrary, 'not useful or slightly useful' videos about breast self-examination and gallstone disease were reported to be watched more than useful videos, which Lee et al. attributed to the long duration of useful videos (14, 19). Also, Biggs et al. reported less frequent viewing of rhinosinusitis videos that were scored to be useful but had longer duration (27). In video analysis studies about bariatric surgery and endometriosis, there was no correlation between usefulness score and video length (1, 7). A study on thyroid surgery suggested that the number of views is not related to the quality of the videos and that this will show videos' popularity or videos may be ad-supported (11). Several studies found no association between Quantitative information of videos and the number of likes or dislikes (1, 14, 29). A study about videos describing the management of prostate cancer on YouTube found a significant negative correlation between scientific quality and contribution of viewers (30). In our study, we could not find a relationship between usefulness score and quantitative

information of videos, but the number of views was positively correlated with time passed since video upload, but negative correlation was observed in the rate of likes.

It has been reported that laparoscopic surgery videos are more useful for doctors (31). Kaya et al. showed that Robotic surgery is more educational in endometriosis surgery (7). In our study, robotic surgery as a surgical method was used in only one video and it was classified in the not useful group.

The limitations of our study; It is not possible to measure the interest and knowledge level of the users; however, it cannot be determined whether the videos that the users access meet needs in their education.

CONCLUSION

YouTube videos are inevitably used as complementary tools in surgical training. However, even if the uploaded videos are uploaded by healthy professionals, the overall rate of useful videos is low. We think that useful videos are not related to quantitative information of video, therefore have to be watched based on keyword relevance priority. Research in this area is still in its initial phase and needs new points of views.

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Examination the effects of chestnut and Manuka Honey for wound healing on mice experimental model

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ABSTRACT

Objective: In this study, the aim is to examine the effects of Chestnut and Manuka honey on wound healing in order to investigate the effectiveness of cost-effective alternative to current approaches in terms of wound care and treatment.

Material and Methods: In this study, we used 30 healthy male Balbc mice weighing 18-24 g. We randomly divided the rats into three groups. A control group, a group treated with only Chestnut honey, a group treated with Manuka honey cream. After the wounds were formed in groups, the tissue samples were gathered on the seventh and fourteenth days. Then these samples were examined histologically and immunohistochemically.

Results: When the study results were evaluated, statistically significant differences were seen between histological and immune-histochemical findings in wound tissue preparations. On the seventh day, tissue samples showed re-epithelialization ($P=0,002$), granulation cell density ($P=0,003$) and angiogenesis ($P=0,003$). In the fourteenth day tissue samples, we found epithelialization ($P=0,001$), granulation cell density ($P=0,002$) and angiogenesis ($P=0,001$). In the tissue samples in the seventh and fourteenth days between the groups, we found immuno-histochemically, Ki-67 and EGF dyeing percentages as $P=0,004$ and $P=0,003$ respectively.

Conclusion: We think chestnut honey may contribute to a shorter wound healing process.

Keywords: Honey, Wound Healing, Re-Epithelialization

INTRODUCTION

Wound formation is defined as the permanent or temporary loss of histological and physiological properties when the tissues are exposed to a force greater than they can tolerate (1). Also, wound formation is a process that socially limits the quality of life of patients and increases the cost of treatment, affecting not only the patient but the whole society (2). In the past, the aim was to bring the wound lips closer together to allow the wound to heal quickly in the treatment of surgical wounds. In current approaches, it has been understood that a moist and warm environment to be created around the wound is more effective in wound healing (2). Thus, it is based on the idea that this situation creates an ideal environment for wound healing and that epithelial cells can move freely (3). In addition to being a topical agent, honey has a low treatment cost. Along with its antibacterial properties, honey is also used as a wound healer. By keeping the wound moist, it allows epidermal migration and it provides trace elements that are effective in healing. It also stimulates the release of inflammatory cytokines from macrophages. All kinds of honey can be effective in wound healing. Jellybush or Manuka honey is obtained from the plant named ocean sturgeon and it is known to have high antibacterial properties together with Jambhul honey from India (2). In a systematic review by Yaghoobi et al., it was observed that honey has a similar effect compared to conventional treatments in the treatment of acute wounds and superficial-partial thickness burns (4). In another study on mice; Acacia honey was used in wound treatment and a positive increase was found in granulation tissue, collagen synthesis and wound healing (5). Studies showing that the use of honey is effective in the healing of chronic wounds and accelerates healing have been reported (6, 7).

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Considering the plant existence, endemic species, medicinal aromatic plants and wide range of varieties in our country, there are many possibilities that can be used for the benefit of medicine. In the literature review, no findings or studies were found regarding the effectiveness of Manuka Honey and Chestnut Honey of Western Black Sea Origin on wound healing. However, the comparison of the effects of Chestnut Honey from Western Black Sea, which is likely to be among the natural treatment alternatives in wound healing, with Manuka Honey on wound healing performance will be a unique study.

In this study, the aim is to examine the effects of Chestnut and Manuka honey on wound healing in order to investigate the effectiveness of cost-effective alternative to current approaches in terms of wound care and treatment.

MATERIAL and METHODS

This study was conducted by Sakarya University Animal Testing Local Ethics Committee approval in Sakarya University Experimental Research and Medical Centre (Dated 12/01/2022 and numbered 02). The procedures on the rats were humane, and the standards of the study were pertinent to the standards of the existing ethical animal testing procedures.

Experimental Animals

In this study, 30 healthy male BALB/c mice weighing between 18-28 grams were used as experimental animals. This experiment was conducted in Sakarya University Experimental Research and Medical Center (Sakarya, TURKEY). The mice were fed with water and ad libitum according to standard diet (Arden Research& Experiment, Ankara, TURKEY). Mice were kept at 21 ± 1 °C in well-ventilated places within 12- hour day-night cycle.

Experimental Protocol

We randomly divided the mice into three groups as spontaneous recovery, Manuka honey and chestnut honey groups. The decubitus ulcer model was used by Stadler et al. (8). The rats were anaesthetized by first Ketamine HCL 100 mg/kg IM (Ketasol %10, 10ml) (Ketasol, Richterfarma, Austria) and then Xylazine 10 mg. The hair between the two blade bones of the rats was shaved. Following the cleaning of the wound site, each mouse was wounded in a circular shape with a 5 mm diameter sterile punch biopsy instrument excisionally, into the superficial fascia to include all layers of the epidermis and dermis. The wound creation was done by the same person each time. After the skin defect was created in mice, the wounds were wiped with serum physiological before dressing, and this process was repeated during each dressing change. Wound care was performed every day for 14 days following the application while the day of wound formation was accepted as the day zero of the application. The standardized forms of animal and herbal products to be applied to wounds were used. In addition to these, the tissue samples from all groups were taken for the examination in the light microscope on the 7th and 14th days of the surgical intervention.

Histopathological Evaluation

Tissue samples were collected from wounds on the seventh and fourteenth days of the decubitus ulcers. The tissue

samples were immobilized in the formaldehyde buffered 10% for 48 hours. The tissue sample was soaked in paraffin-embedded blocks after the tissue embedding processes. The preparations were stained with Hematoxylin-Eosin (H-E) for histological examination. According to "The Wound Healing Points Evaluation Criteria" a histologist evaluated histopathological examinations (9).

Immunohistochemical Staining Method

After the deparaffinization of the tissues placed on a slide with "Poly-L-Lysine", 4 µm thick sections from tissues fixed in neutral formaldehyde solution were boiled in a citrate buffer for antigen retrieval for 20 minutes in a microwave oven. For endogenous peroxidase inactivation, they were incubated with 3% hydrogenperoxide (H_2O_2) for 20 minutes after PBS bath. After cooling, K \dot{I} -67 (sc-52746, Santa Cruz, USA), IL-6 (sc-32296, Santa Cruz, USA), EGF (sc-52012, Santa Cruz, USA), primary antibodies were used as primary antibody and the rat and rabbit specific HRP/DAB detection IHC kit was used as secondary antibody. Immuno-positivity in samples was evaluated after counterstaining with hematoxylin by giving

a semi-quantitative number for positive cells. In all groups, at least 200 cells were marked within each x40 magnifying area. In incisions, the percentage of the stained cells and staining level were the criteria to be chosen. For each incision, immune-histochemical staining scoring was calculated according to H-SCORE, which is a scoring algorithm formulated as $(I \times PC)$, (I: the level of staining, PC: the percentage of stained cells in each level) (10).

Statistical Analysis

Statistical analyses were performed using the SPSS 24.0 package program (SPSS Inc. and Lead Tech. Inc. Chicago. the USA). Shapiro Wilks test was used in compliance with normal distribution. Kruskal Wallis test was used for numerical data of the subgroups that did not show normal distribution. Intergroup evaluations for statistically different parameters were performed using the Mann-Whitney U test and comparing them in pairs. Results were given as mean \pm standard deviation. For all statistical analyses, a two-tailed P-value <0.05 was considered statistically significant.

RESULTS

When we compared the 7th and 14th day tissue samples of the control, Chestnut and Manuka honey groups in terms of reepithelialisation, statistically significant differences were found between the tissues of both days for the groups (P values in order $p=0.002$; $p=0.001$). On the 14th day, it was observed that the reepithelialisation was completed in the chestnut and Manuka honey groups, but not in the control group. On the 7th day, it was observed that the formation of reepithelialisation in chestnut honey was quite ahead of Manuka honey group ($p=0.006$). It was observed that reepithelialisation was more advanced on the 7th day in chestnut and Manuka honey groups than in the control group (P values in order $p=0.002$; $p=0.001$) (Figure1).

When we compared the control, Chestnut and Manuka honey groups in terms of granulation cell density on the 7th and 14th days, it was seen that the granulation cell density was lower in the Chestnut honey group than the Control and Manuka

honey on both the 7th and 14th days. Statistically significant differences were observed between the groups. (P values for the 7th and 14th days, respectively, $p=0.004$; $p=0.002$). When compared with Chestnut honey group ($p=0.000$) and Manuka honey group ($p=0.000$), the granulation cell density the control group tissue samples were observed to be more on the 7th and 14th days. This showed that wound healing was slower in the control group. The same situation was also observed in the Chestnut honey and Manuka honey groups on the 14th day and 7th day. Statistically significant differences were seen on the 7th and 14th days (P values $p=0.000$ and $p=0.006$, respectively) (**Figure1**). Likewise, statistically significant differences were observed in Chestnut honey and Manuka honey groups on the 14th day compared to the 7th day. P values, on the 7th day $p=0.000$ and on the 14th day $p=0.006$ (**Figure1**).

When we compared the tissue samples of the control, Chestnut and Manuka honey groups in terms of angiogenesis rates, it was observed that the tissue samples on the 14th and 7th day created statistically significant differences between the groups on both days (P value respectively $p=0.003$; $p=0.001$). In the chestnut honey group, angiogenesis was found to be higher than Manuka honey and control groups on the 7th day (P values respectively $p=0.005$ and $p=0.001$ (14). The intensity of angiogenesis in the chestnut honey group on the 14th day was lower than Manuka honey and control groups (P values respectively $p=0.006$ and $p=0.001$). Manuka honey group had a higher angiogenesis rate on the 7th day than the control group, but on the 14th day, angiogenesis was observed at higher rates in the control group than Manuka honey group. Statistically significant differences between the two groups were observed on the 7th ($p=0.002$) and 14th ($p=0.000$) days. (**Figure1**).

We stained the tissue samples on the 7th and 14th days of the standard and Western diet groups with Ki-67 and EGF antibodies separately and evaluated the results. The percentage of Ki-67 staining in the tissue samples of the Chestnut honey group on the 7th day was higher than that of Manuka honey and control groups. P values were $p=0.015$ with Chestnut-Manuka honey and $p=0.001$ with chestnut honey-control group, respectively. On the 7th day, the least percentage of Ki-67 staining was seen in the control group. On the other hand, the percentage of Ki-67 staining in the chestnut honey group was seen at a lower rate in the wound tissue samples on the 14th day compared to the 7th day. The highest percentage of Ki-67 staining on the 14th day was seen in the control group. Statistically significant differences were observed between the control group and Chestnut honey group ($p=0.003$). There was no statistical difference between the percentage of Ki-67 staining on the 14th day of Chestnut honey and Manuka honey groups ($P>0.05$). Statistically significant differences were also observed in the percentage of EGF staining between the groups on the 7th and 14th days ($p=0.000$). On the 7th day, the highest percentage of EGF staining was observed in Chestnut honey group. The lowest was observed in the control group. Statistically significant differences were observed in Chestnut honey- Control group ($p=0.000$), Chestnut honey- Manuka honey groups ($p=0.011$). On the 14th day, the highest percentage of EGF staining was seen in the Control group while no statistically significant differences were observed between Chestnut and Manuka honey groups ($p>0.05$). Statistically significant differences were observed between the control group- chestnut honey group ($p=0.002$) and the control group- Manuka honey group ($p=0.003$) (**Figure1**).

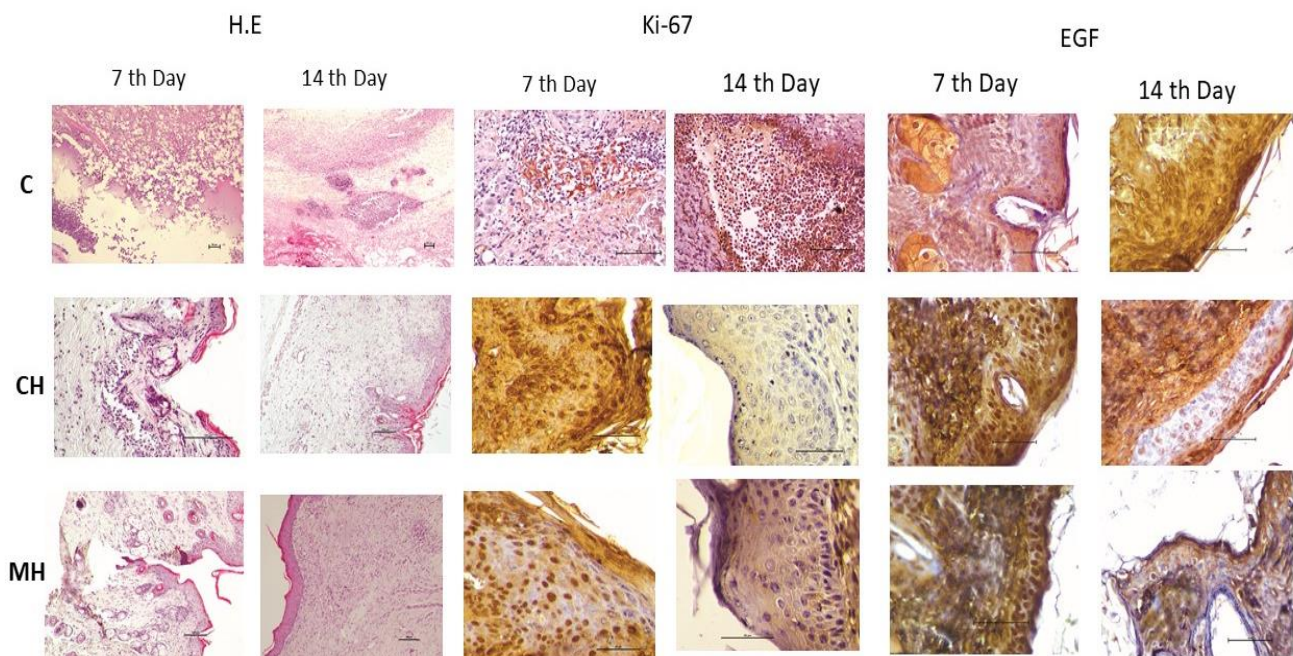


Figure1. Histopathological comparison between groups, X100. As a result of both H.E and immunohistochemically coloring KI-67 and EGF; In the CH group, a faster remodeling occurs in the 7th days than in groups MH and C. In group C, recovery and remodeling were seen at the latest. C: Control, CH: Chestnut Honey, MH: Manuka Honey. H.E.: Hematoxyline Eosin. EGF: Epidermal Growth Factor.

DISCUSSION

Honey contains sugar, enzymes, flavonoids, minerals and other nutrients. It has antioxidant, anti-inflammatory properties and it has been used in wound treatment to promote rapid healing or healing support (11, 12). In addition to the epithelium in the wound area, myofibroblasts, collagen and angiogenesis play important roles in wound healing (11, 12, 13, 14). Collagen is the main structural component of the extracellular matrix and it plays a vital role in maintaining the integrity of all tissues and wound healing (14, 15). Angiogenesis refers to the formation of new blood vessels at the wound site and it is a necessary component of the healing process due to increased nutrient requirements (16). In our study, we evaluated the healing process of Chestnut and Manuka honey in the wound area. For this purpose, we performed our observations by mutually evaluating the histological properties of epithelialization, granule tissue density and angiogenesis parameters in wound tissues and the intensities of Ki-67 and EGF staining immunohistochemically.

In a previous study, it was reported that reepithelialisation in the wound area occurred more quickly in the wound healing phase of Manuka honey and Indonesian honey compared to the control group (17). In a study conducted with rabbits, chestnut, flower and rhododendron honeys were used in wound treatment. Very high reepithelialisation rates were observed on the 7th day, and it was observed that the epithelialization was completely realized on the 21st day (18). In our study, there was no difference in reepithelialisation between Chestnut and Manuka honeys on the 14th day. However, on the 7th day, reepithelialisation was more advanced in Chestnut honey than in Manuka honey group. We observed that reepithelialisation was faster in Chestnut honey group. On the 14th day, except for the control group, epithelialization was completed in the honey groups. From this perspective, our study is similar to the studies in the literature (17, 18). It is reepithelialisation that starts a few hours after injury in wound healing, but it shows more pronounced activity in the proliferative phase and it can continue until the extracellular matrix remodelling phase (19). Epidermal growth factor (EGF) is an important indicator of this phase and has mitogenic and migratory activity in border keratinocytes (20). In our study, the highest intensity of EGF positive staining was observed in Chestnut honey group on the 7th day in the scar tissue samples, and the lowest staining was observed on the 7th day in the control group. On the other hand, EGF positive staining intensity was the same in Chestnut and Manuka honey groups on the fourteenth day. Epithelialization was completed in these two groups. EGF positive staining results were lower and epithelialization was not completed fully in the control group on the fourteenth day. Our IHC staining results showed parallelism with our H.E. staining results.

In literature, it has been reported that honey and especially Manuka honey have positive effects on tissue healing, tissue formation, capillary vessel modelling and increasing collagen synthesis in wound healing stages (17, 21). In our study, on the 7th day, granulation and angiogenesis in the chestnut honey group showed differences compared to Manuka and the control groups. An intense formation was observed in Chestnut honey group. On the 14th day, no difference was

observed in Chestnut and Manuka honey groups while a slow progress was observed in the control group. The rapid recovery status of chestnut honey group on the seventh day differed from studies in the literature (5, 18, 21). The formation of granulation tissue formed by macrophages, fibroblasts and neoforms is essential for the reepithelialisation process and tissue restructuring (19). Increased cell proliferation is an important aspect of wound healing in general, and Ki-67 protein is an important indicator of this cellular event.

Ki-67 expression is also commonly an indicator of cell growth in a total cell population (22). In our study, it was observed that Ki-67 positive staining was quite high in Chestnut honey group on the 7th day. It was also high in Manuka honey group, but still lower than Chestnut honey group, and the lowest level was observed in the untreated control group. On the 14th day, Ki-67 expression was in the control group because the wound healing process continued. On the 14th day, Ki-67 level was quite low in Chestnut and Manuka honey groups. We think that this is due to the fact that the healing process is faster in honey groups. Ki-67 protein positivity results were found to be similar to the granulation and angiogenesis results.

CONCLUSION

The results obtained from this study show that honey used for therapeutic purposes in wound healing is effective in the healing process. In addition, Chestnut honey was found to be more effective than Manuka honey in wound healing. For this reason, the botanical origin of honey is extremely important in terms of productivity. Application time also affects wound healing. Based on the results from this study, new prospective studies with different honey types, animal models and dosages can be planned.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

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Relationship between Refractive State and Nutritional Status among the children

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ABSTRACT

Objective: Refractive error and malnourishment both are common issues in developing countries therefore in this study main aim is to find the relationship between refractive state and nutritional status.

Material and Methods: This was a cross-sectional observational study conducted at Tehsil Headquarter Hospital Kamoke. The sample size was 200 children equally divided into well-nourished and malnourished groups with their age range between 3-12 years of both gender. First visual acuity was measured monocularly with Snellen's Chart. The amount and type of refractive error were assessed using cycloplegic refraction with cyclopentolate 1% eye drops. Eyes with amblyopia, strabismus and any other ocular pathology that affects vision were excluded. All children were referred from eye department to the nutritionist of this hospital to determine the nutritional status through WHO provided guidelines.

Results: There were a total of 101 (50.5%) males and 99 (49.5%) females in this study. The most common type of refractive error was Astigmatism which was present in 29 (29%) well-nourished and 31 (31%) malnourished children. The least common was hypermetropia which was present in only 3 children and all were females. However, myopia was present in 12 (12%) well-nourished and 11 (11%) malnourished children.

Conclusion: Thus, Refractive errors were present in both groups. The most common was Astigmatism and the least common was hypermetropia in both groups. The inferential statistics of this study concluded that refractive errors were not related with nutritional status but may be due to some factors.

Keywords: refractive state, nutritional status

INTRODUCTION

Vision plays an integral part in effective communication and learning. Eighty-five percent of visual information is received from the environment (1). According to the World Report on Vision, globally, at least 2.2 billion people have vision impairment or blindness. At least 1 billion have a vision impairment that could have been prevented or has yet to be addressed (2). Uncorrected refractive errors are a common cause of visual impairment worldwide (3, 4). Refractive errors are not equally distributed in countries. Prevalence of un-corrected refracted error was more in developing countries about 90%. Myopia is more common and has more prevalence in East Asian countries. Hypermetropia is more prevalent in Europe and western countries (5, 6).

Uncorrected refractive errors affect children's daily life due to poor vision, inability to perform daily activities, psychological problems and leading strabismus, anisometropia and amblyopia (5, 7). Generally, children do not complain about decreased vision and may not be aware of their problems. They may adapt their defective vision through strategies such as changing the classroom environment, bringing things closer, and paying attention to avoid tasks that require a lot of visual focus (3, 8).

Risk Factors associated with refractive error among children defined as the duration of watching television, mobilephone usage, the distance between children and television, a study in inadequate light and positive family history of refractive errors (9, 10).

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The relationship between visual impairment and poor diet has been recognized previously (11). Results indicate to that, nutrition plays an important role in the development of refractive errors (12). It has a profound effect on the development of future generations (13). Also, Globally visual impairment and malnourishment are major public health issues among school children leading to morbidity and mortality (14, 15). Especially, malnutrition is a burden in South Asian countries like India, Pakistan and Bangladesh as more than half of the children affected by malnutrition live in this regions (16, 17). It is estimated that, 428 children out of every 100,000 children aged <5 years of age are considered malnourished in Pakistan (16, 18). Therefore, this study aims to find the effect of nutritional status on refractive state of children.

Young children are living in extreme poverty conditions mostly affected by malnutrition with greater intensity due to low socio-economic status, environmental factors, political and cultural and educational background (19). Even if, refractive errors cannot be prevented but can be diagnosed early with regular eye examinations (1, 20). Therefore, experts recommend that the children should be screened for early detection of refractive errors (3, 8).

MATERIAL and METHODS

This study is a cross-sectional, case-controlled observational study which conducted at the "Department of Ophthalmology" of Tehsil Headquarter Hospital Kamoke, Pakistan during August and September, 2021. Helsinki (2008) principles were followed to conduct the study. Based on the study's objectives, a sample frame of 200 children was drawn by equally dividing into two group. Group one was a well-nourished group, and the Group two was malnourished. Both groups had similar characteristics of age, gender, economic status and demographic conditions.

The inclusion criteria for the study were set to be age range of 3-12 years, of either gender, present to OPD with blurring of vision or for visual screening and having best-corrected visual acuity (BCVA) of 6/9 or better on post-cycloplegic subjective refraction. Children with amblyopia, strabismus, ocular trauma, ocular pathologies that affect vision and age of less than 3 years and more than 12 years were excluded from the study.

All of the two hundred children have in the inclusion and exclusion criteria. After applying exclusion criteria, consent was taken from parents before collecting the data. A detailed anamnesis, including duration of blurring of vision, history of spectacles use, have been obtained. The visual acuity was checked monocularly by using Snellen's visual acuity chart at 6 meters. In case of substandard vision, pinhole test was done to assess the maximum improvement after correction. Amount and type of refractive error were assessed with cycloplegic refraction by using cyclopentolate 1% eye drops. For adequate cycloplegia and mydriasis, the cycloplegic drug was administered three times with the interval of 10 minutes and objective refraction was examined by using streak retinoscopy after 90 minutes of first drop. After 3 days of cycloplegic refraction, post cycloplegic subjective refraction in verbal children based on retinoscopy findings was measured.

The children were considered emmetrope if their visual acuity is 6/6 and require no correction. Myopia was considered as a refractive error requiring a minus sphere of 0.50 Diopter or more for correction and hyperopia if need a plus sphere of 1.00 D or more and Astigmatism with the cylindrical correction of ± 0.50 or more. Children who have different refractive states were recorded.

Strabismus was assessed by Hirschberg test, Cover-Uncover test and Extra Ocular Motility. Ocular pathology was ruled out by anterior and posterior segment examination via Slit Lamp Biomicroscopy and Fundoscopy.

The children were divided into case and control groups based on their nutritional status. Therefore, all children were referred from Department of Ophthalmology to the Nutritionist of Tehsil Headquarter Hospital, Kamoke, to find out their nutritional status and instruct them to report back again in Ophthalmology department. The Nutritionist made the diagnosis as the child is malnourished or nourished by two methods. First through Outpatient Therapeutic Program for children from 3 to 5 years of age and the second is WHO guided table used for children of age more than 5 years.

Data were recorded for each child in a Microsoft Excel file. After collection of data, the data was transferred into the SPSS and results were analyzed and organized by using SPSS 26 and Microsoft Excel. Descriptive and inferential statistical techniques were adopted to investigate the data and draw information based on data.

RESULTS

The total sample of 200 children's data was divided into different age groups. It was found that 99 (49.5%) children belonged to 9-12 years of age. However, 37 were included in 3-5 years of age while 64 children belonged to 6-8 years of age which were 18.5% and 32% respectively of the total sample.

The sample was equally likely divided into two clusters, well-nourished and malnourished. The group well-nourished was set as the control group and the malnourished group was set as the case group.

There were 101 (50.5%) boys and 99 (49.5%) girls in the total sample size. The sample was approximately equally divided into male and female representation.

In this study, the Emmetropia among boys and girls is common and amazingly equal in both malnourished and nourished groups. Most of the children belonged to 9 to 12 years of age group. Out of 114 (57%) emmetropes, 53 were from age group 9 to 12, 20 were from age group 3 to 5 and 41 were from age group 6 to 8. Well-nourished male children were leading in count as compared to well-nourished female children. Among the well-nourished group, out of total 58 were emmetropes among them, 31 were males, and 27 were females. However, in malnourished group emmetrope, the female count is slightly higher than the male count.

Myopia was present in 23 (11.5%) children, in which 14 were females, and 9 were males. Among 9 males, 7 were fully nourished, while 2 were malnourished. However, out of total 14 myopic females, 5 were well-nourished while 9 females were malnourished. Most of the children belong to the 9 to 12 years age group; 21 children were belonging to this age group

and 2 were from age group of 3 to 5 years. Hence, myopic girls were leading in count compared to boys in the nourished group while boys were dominant in count among the malnourished group.

The hypermetropic children were only 3 (1.5%) in the count, and all were girls. No Hypermetropia was seen in males either they are well-nourished or malnourished. However, one female from the control group belongs to the age group of 3 to 5 years while two females from the malnourished group belonging to 6-8 years age group were hypermetropia.

Astigmatism was present more among males of both groups. Astigmatism was present in 60 (30%) children, out of which 25 from 9-12 years age group, 14 from age group 3 to 5 years and 21 from age group 6 to 8 years. Sixteen well-nourished males and 19 malnourished males had Astigmatism. However, among the female of both groups, there were 13 well-nourished and 12 malnourished children.

Pearson correlation was used to check the degree of association between the refractive state and the nutritional state. The Pearson correlation coefficient (0.026) and Spearman correlation coefficient (0.023) were very low. Results show that the refractive state and nutritional state of children does not have a favourable relation. In other words, the degree of association between child's refractive state and nutritional status has nothing to do with each other. We cannot say that children with specific nutritional status are likely to have a refractive error based on the calculated value of the coefficient of correlation.

The Chi-Square tests results were insignificant, which shows a very weak association between refractive errors and nutrition status of children aged 3 to 12 years. Both incidents were independent of each other, or we are failed to establish an association between both conditions significantly (Chi-Square= 0.479, P value= 0.924).

Table 1: Comparison of Nutritional Status by Gender and Age

Nutritional Status	Age	Gender		Total
		Male	Female	
Fully Nourished	3-5 years	18	10	28
	6-8 years	13	16	29
	9-12 years	23	20	43
	Total	54	46	100
Malnourished	3-5 years	3	6	9
	6-8 years	19	16	35
	9-12 years	25	31	56
	Total	47	53	100
Total	3-5 years	21	16	37
	6-8 years	32	32	64
	9-12 years	48	51	99
	Total	101	99	200

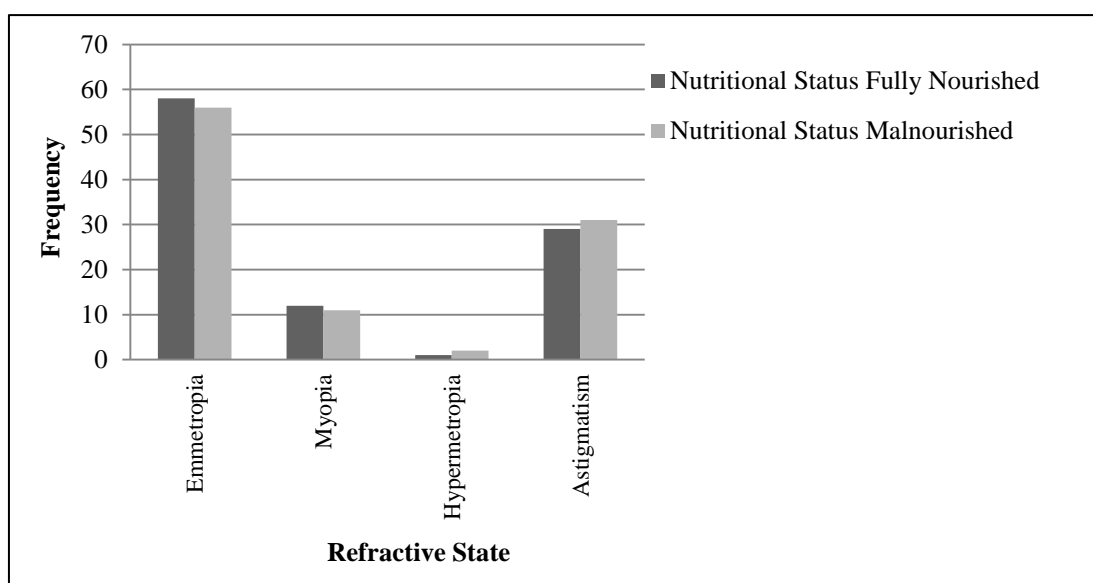


Figure 1: Refractive State Versus Nutritional Status

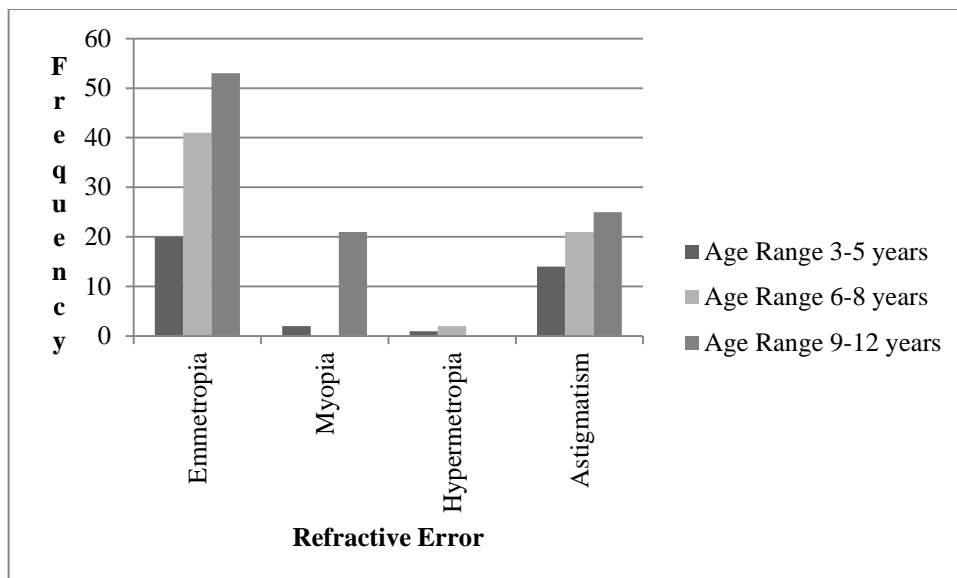


Figure 2: Age wise distribution of Refractive error

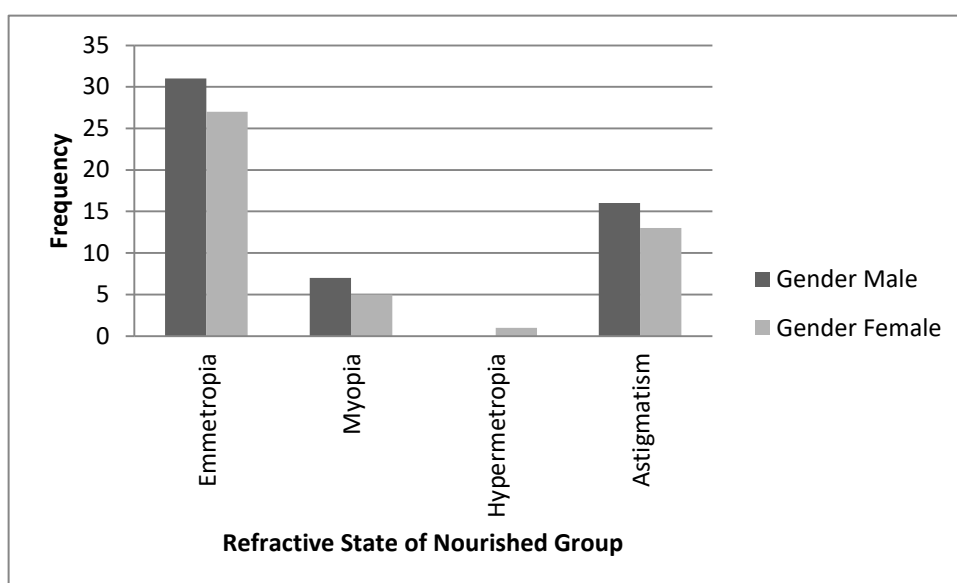


Figure 3: Gender wise distribution of Refractive State in Well-nourished Children

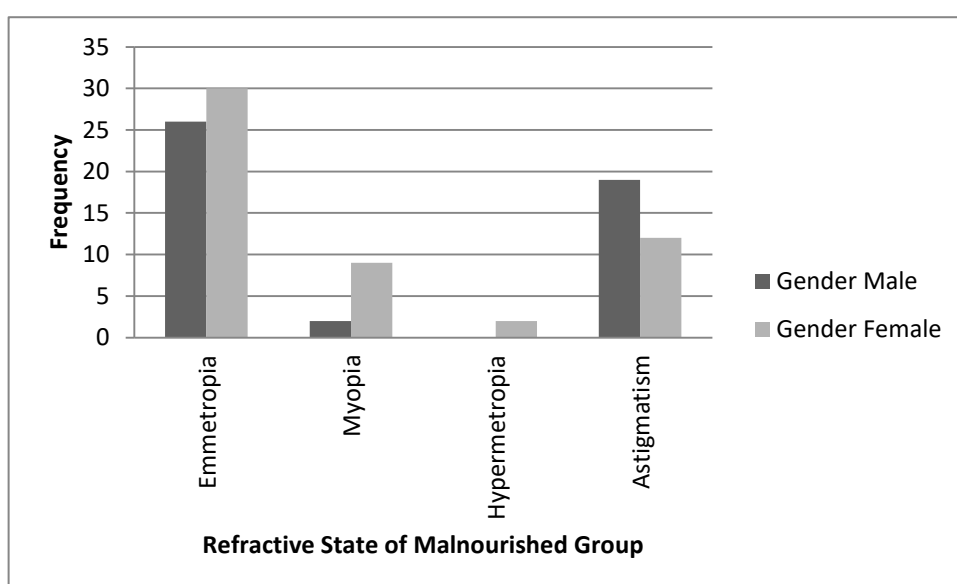


Figure 4: Gender Wise Distribution of Refractive State in Malnourished Children

DISCUSSION

Vision is the initial source of information in the human body. It is the door to getting knowledge and understanding of surroundings for newborns and early childhood. For children's proper intellectual development and smart decision-making ability, vision plays a key role in collaboration with other senses. In accessing health and quality of life, sight is among the important indicators. With excessive use of technological learning aids like the use of multi-media in schools, online classes, and tremendously increased on-screen time, especially in children have increased visual requirements. Accurate vision ability of the eye at an early age and its proper development is essential for further intellectual growth. The most common blip of an eye in school going children is a refractive error.

In the present study, in the total sample of 200 children, males were 101, while 99 were females with the age range between 3 to 12 years. Among them, 114 (57%) were emmetrope, 23 (11.5%) were myope, 3 (1.5%) were hyperope and 60 (30%) astigmatism. Astigmatism was found as major refractive error in both fully and malnourished group. However, the previous study conducted by Sajid Munir, Hussain Sherazi, Rehman, et al. found that myopia (40%) was the major refractive error above 5 years of age and hypermetropia (24%) was the major refractive error below 5 years of age (21).

The Refractive state of the eye seriously affects learning and creates difficulty (22). Another problem that is evident in children is malnutrition (23). Most diseases such as the refractive state in children, are due to a lack of nutrients in the diet.

Growth in the human body is subject to certain dietary requirements. If a diet is lacking the required amount of essential nutrients, such a condition is called malnutrition. Malnutrition leads to deficiency the optimal functioning of the human body and makes humans vulnerable to diseases. Most diseases in children are due to the lack of a balanced diet. By balanced or healthy diet, the diet means that contains adequate quantities of certain nutrients, minerals, proteins, and vitamins. Most body organs are in the development phase in early childhood, so the importance of a balanced diet becomes more prominent for the proper development of body organs.

Most of the children goes to school without breakfast. The reason is increasing of the use of junk food, children may sleep at late night. So, in the morning, they may not be able to go to school in good health (21). In this study, more females (53) were malnourished, and maximum frequency was found in the age range between 9 to 12 years, however, more males (54) belong to the well-nourished group with maximum number of children in 9 to 12 years of age group. Emmetropes were 58 and 56 in number in well-nourished and malnourished groups, respectively. Twelve myopes were found in fully nourished, and 11 were in the malnourished group. Hypermetropia was rarely observed and found among only 3 females, 1 children was in well-nourished group and 2 children were in malnourished group. Astigmatism was observed in 29 well-nourished children while among 31 malnourished children. While in a previous study, 16% of subjects with a diet poor in protein, fruits and vegetables and high in carbohydrates have poor visual acuity (24).

Moreover, in another previous study, higher frequency of hypermetropia 97 (55.1%) and emmetropic children 10 (5.7%) were found in the control group while myopia 3(1.6%) and astigmatism 94 (51.6%). Astigmatism was more prevalent in the studied group. Dantas, Brandt, & Leal was not found any biomicroscopic changes in the control group, however, biomicroscopic changes were detected in the malnourished group. Their study favours that early malnutrition effectively interferes with the visual health of individuals (19).

CONCLUSION

This study did not find any gender-specific pattern of refractive error depending on nutrition status. The refractive errors were present in boys and girls without any significant gender inclination. Among the children between 3 to 12 years old, the most affected age group was 9 to 12 years old. Among the three types of refractive errors, the most common refractive type was Astigmatism. Hypermetropia was the rare type of refractive type among children of both well-nourished and malnourished groups. Children aged between 3 to 12 years old are equally likely vulnerable to the incident of refractive error irrespective of their nutritional status. As an obvious result of statistics, there is no relation between the refractive error problem and nutritional status among the children. Based on our study results, we can say that there may be other factors than a nutritional status that are the main cause for the refractive error among the children.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

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Family Factors and Major Depression in Macau Adolescents

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ABSTRACT

Objective: Aim of this study is to investigate the current condition of adolescent depression in Macau and its relation with family factors, and to provide a reference for formulating policy about the issue

Material and Methods: The study used randomised multistage stratified cluster sampling. In March 2021, all students in normal education from Form 1 to Form 6 in day Secondary schools were eligible for study sampling. Patient Health Questionnaire-9 (PHQ-9) used to assess depression severity and a self-formulated questionnaire for investigation of family-related factors..

Results: There was total of 939 validated questionnaires, major depression occurred in 16.4% of the study samples, more females had depression than males (21.8% and 11.4%, respectively). Among all family factors, low-income family financial condition (monthly income <10000 MOP) (OR=2.71, 95% CI 1.02-7.21), parents not caring (OR=2.18, 95% CI 1.01-4.69), poor relationship with parents (OR=3.01, 95% CI 1.53-5.91) and often quarrel with parents (OR=3.39, 95%CI 2.12-5.42) had significant correlation with adolescent major depression. The study also noted that female adolescents with major depression were more affected by family factors.

Conclusion: According to study results, Family factors and adolescent depression has correlation, it is advised that family intervention can be used as a reference for strategies on improving the adolescent depression problems.

Keywords: Depression, adolescents, family relationship, Macau

INTRODUCTION

Depression is a major mental health concern worldwide. In 2015 World Health Organization (WHO) ranked depressive disorders as the third cause of Disability Adjusted Life Year (DALY) in global adolescents aged 10-19 years old. Within the age 15-19 years group, depressive disorder ranked even higher as the second on the global causes of DALY, only after road injury (1). The most severe consequence of depressive disorders is death by suicide. The link between suicide and depression is well-known. About two-thirds of all depressed patients contemplate suicide, while 10 to 15 percent commit suicide (2).

In Macau, the Centre of Disease Control and Prevention (CDC) conducts a survey on health behaviours in secondary students regularly. In the school year 2017-2018, 13.7% of the students mentioned feeling unhappy or desperate most of the time for at least 2 weeks in the past year. (3) Since this is one of the core symptoms of major depression (4), it is not known whether the students were suffering from a major depressive episode. From 2013 to 2018, suicide attempts have doubled among Macau secondary students (3, 5). This may suggest an increase in major depression. However, there is no data on the prevalence of major depression in Macau adolescents.

With an area of 32.9 km² and a total population of about 680,000, Macau is the most crowded place in the world (6). The historic city is in the UNESCO Cultural Heritage list, famous for a mixture of Chinese and Portuguese culture. On the contrary, we are also densely packed with the 24/7 running casinos. With the huge amount of income coming from the gambling business, Macau is the second rich region in Asia in terms of GDP (PPP) per capita (7).

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Since many people work in the gambling or hotel business, many parents need to be on shift. This would definitely decrease the time of being with their children. Reducing time in communication is likely to affect the relationship. All the above situations could have contributed to major depression picture very different from other parts of the world. This study has been designed to assess for major depression in Macau adolescents with results on a validated screening tool for the condition. In addition, we would also like to examine the association between different family factors and major depression among the adolescents. We hypothesise that the development of major depression in adolescents is related to family background and the adolescents' relationship with their parents. To our knowledge, studies on the condition of adolescent depression is lacking in Macau, this is the first study done on the association between family factors and adolescent major depression in Macau. With this study, we aim to provide data that would be of use in future for local Public Health strategies in the prevention and management of adolescent depression.

MATERIAL and METHODS

General Study Information

The Study is one part of a cross-sectional study named "Alcohol Use in Macau Secondary Students---a Study on Knowledge, Belief and Behavior of Alcohol Use and their Correlating Factors". In the survey, students of age 11-20 were asked to fill in a questionnaire which contained a total of 73 questions on 7 different parts. This included background information, knowledge about alcohol use, beliefs towards alcohol use, behaviors of alcohol use, family factors, peer factors and mental health condition. Parental consents were obtained for the participation of the students under the age of 18.

The survey was conducted during class time in secondary schools from 28th of March, 2021 to 2nd of April, 2021. A pre-test was conducted on 1st of March, 2021 to establish the validity and reliability of the questionnaire. The questionnaires were filled anonymously with written instructions on the aim of the study.

Since Macau has a 15 years free education scheme, almost all adolescents are enrolled in secondary education except for rare cases such as those having chronic illnesses or disabilities that prohibited them from attending school. A school-based study could be assumed to be highly generalisable to Macau adolescent population as a whole.

Assessment of major depression

The Chinese version of Patient Health Questionnaire-9 (PHQ-9) was implemented in the aforementioned questionnaire for the assessment of the mental health condition. The PHQ-9 is a self-administered instrument that was developed to measure the severity of an individual's depression by evaluating the depressive symptoms experienced by the individual in the past 2 weeks, using the 9 criteria of major depression listed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (8). There are 9 questions and the answers to the questions are given on a 4-point Likert scale from score 0 for "not at all" to score 3 for "nearly every day", summing up a total score ranging from 0-27.

The higher the score, the more severe the depressive symptoms. According to the recommendation by the developers of the PHQ-9, depressive symptom scores can be classified by severity into five groups, namely, minimal depression (scores of 0-4), mild depression (5-9), moderate depression (10-14), moderately severe depression (15-19), and severe depression (20-27) (8). The PHQ-9 has also been validated as a reliable screening for adolescent depression in both Hong Kong and Taiwan (9,10). In the study in Taiwan, a PHQ-9 score of 15 had a sensitivity of 0.72 and a specificity of 0.95 for recognising major depressive disorder in Taiwan secondary school (9). In our study, we used PHQ-9 score of 15 as a cut off for major depression.

Measures for Family Factors

In the study we looked into the correlation between different family factors and major depression in the surveyed adolescents. The factors include:

(1) Parental divorce

Information came from answers to the question of parents' marital status. The answers included "married", "single", "divorced", "widowed", "remarried" and "others". Adolescents with answers of "divorced" or "remarried" were defined as "having experienced parental divorce".

(2) Parent working on shift

According to the parents' working situation information, the adolescents who responded "need to be on shift" for either father's or mother's work would be defined as having "parent working on shift".

(3) Family poverty

The monthly family salary was classified into different ranges, "<10000 MOP (about USD\$1250)", "10001-30000 MOP", "30001-50000 MOP", "50001-70000 MOP and ">70000 MOP". A monthly family salary of <10000 MOP was defined as "family poverty".

(4) Parents not caring

The information came from answers to the question "do you think your parents care about you?" Answer options included "care very much", "care", "so-so", "not care" and "not care at all". Those who answered "not care" and "not care at all" were defined as the ones who have parents who are "not caring".

(5) Poor relationship with parents

The information came from answers to the question "what do you think about your relationship with your parents?" Answer options included "very good", "good", "not good or bad", "bad" and "very bad". Those who answered "bad" and "very bad" were defined as having "poor relationship with parents".

(6) Often quarrel with parents

The information came from answers to the question "how often do you quarrel with your parents in the current semester?" Answer options included "never", "rarely", "sometimes", "always" and "all the time". The adolescents who answered "always" and "all the time" were defined as those who "often quarrel with their parents".

Sampling, Sample Size and Recruitment Process

In the survey, a total of 24789 secondary students from formal education and vocational education in Macau were eligible for randomisation. It was calculated that at least 648 samples have to be included to achieve a confidence level of 99%, with a sampling error of <5%. Randomisation was done by randomised multistage stratified cluster sampling on school and class bases. Nine hundred seventy-four students from 6 schools and 30 classes were invited to fill-in the questionnaires and 939 valid questionnaires were collected for data analysis.

Data Analysis

Data analysis was performed using SPSS 25.

The χ^2 test for significance in contingency tables was used to identify differences in the studied family factors between adolescents with and without major depression. For the specific factor that was found with a statistically significant difference. Logistical regression analysis (LRA) was further calculated to assess for the extent the specific family factor can predict the presence of major depression. Considering the possible confounding effect of sex and age on adolescent major depression, the LRA calculation was adjusted for sex and age.

RESULTS

Demographic Data

Among the 939 adolescents who filled in the questionnaires and provided data for this study, 491 (52%) were males, and 448 (48%) were females. The age range was 11-20 years old.

Depressive Symptoms Score using PHQ-9

In our study, the mean PHQ-9 score was 8.44 ± 6.12 . Over one-third (36.5%) of the adolescents were found to have moderate to severe depressive symptoms (PHQ-9 score 10-27). Major depression (PHQ-9 score ≥ 15) is found in 16.4% of the adolescents (see table 1).

Higher proportion of females were found to have major depression compared to male (female 24.8%, male 11.4%, $P < 0.001$). There was no difference in the prevalence of major depression in different age groups.

Prevalence of the Family Factors

Table 2 listed the prevalence of the 6 family factors assessed in our study. In the study, 40% of the adolescents have at least 1 parent working on shift. No differences were found between male and female adolescents in the perception of parent's care and relationship with parents. However, significantly more females often quarrel with their parents (F vs M 16.3% vs 9.8%, $P < 0.01$).

Correlation of the Family Factors with Major Depression in Macau Adolescents

Among all family factors studied, 4 of which were associated with major depression in the adolescents (see table 3). These factors included family poverty, not caring parents, poor relationship with parents and often quarrel with parents. Aside from family poverty which is significantly related to major depression only in female adolescents, the remaining 3 factors were related to major depression in both males and females.

The odds ratio (OR) of being classified as major depression with the specific family factor are listed in table 4. Those who had poor relationships with their parents and those who often quarrel with them were 3 times more likely to have major depression than those who didn't report having these 2 factors.

In the study, females are more likely than males to have major depression with an OR of 2.13 ($P < 0.001$). As is shown in figure 1 & 2, the problem of "often quarrel with parents" is the only factor that is associated with increased likelihood of major depression in both adolescent females and males. Female adolescents who often quarrel with their parents were 2.5 times more likely to suffer from major depression, while it is 4.6 times more likely in males.

Table 1. Prevalence of major depression by sex and age, 2021 Macau

Variables	Mean \pm SD (PHQ-9 score)	Major Depression (%)
Whole Sample	8.44 \pm 6.12	16.4
Gender		
M	7.32 \pm 5.81	11.4
F	9.66 \pm 6.23	21.8
Age Group		
11-12	6.46 \pm 5.77	12.0
13-14	7.96 \pm 5.81	14.0
15-16	8.89 \pm 6.35	18.4
17-20	9.24 \pm 6.10	18.3

Table 2. Prevalence of the Family Factors by sex

Variables	M (%)	F (%)	Total (%)
Parental Divorce	11.2	11.4	11.3
Family Poverty	2.7	2.7	2.7
Parents not Caring	3.5	6.0	4.7
Poor Relationship with Parents	4.5	8.0	6.2
Often Quarrel with Parents	9.8	16.3	12.9
Parent Working on Shift	39.0	42.1	40.5

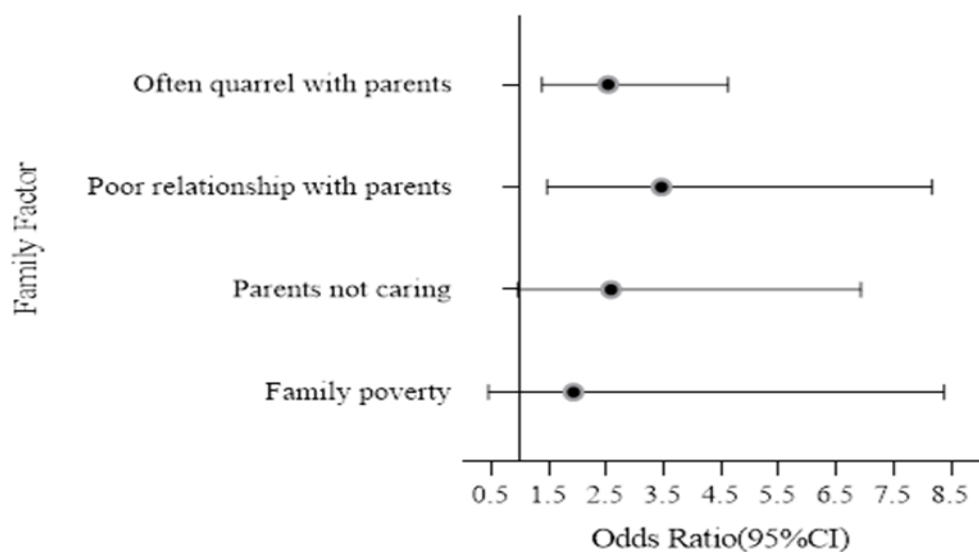
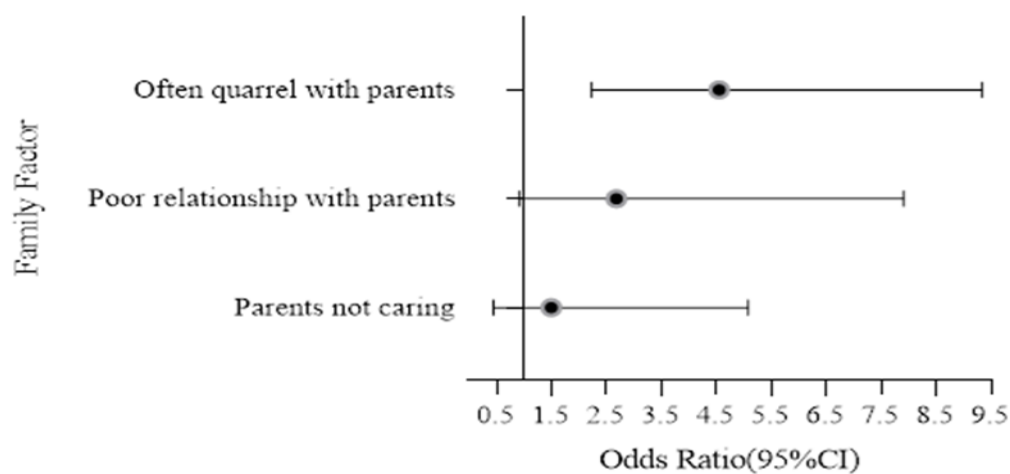
Table 3. Prevalence of the Family Factors in Adolescents with Major Depression by sex

Family Factor	Males (%)	Females (%)	Total (%)
Parental Divorce	1.7	3.0	2.3
Family Poverty	0.8	1.6**	1.2**
Parents not Caring	1.2**	3.8***	2.4***
Poor Relationship with Parents	1.6**	5.1***	3.3***
Often Quarrel with Parents	3.5***	7.6***	5.4***
Parent Working on Shift	4.7	10.1	7.3

p<0.01, *p<0.001

Table 4. Odds Ratio of the Adolescents with Major Depression and a Specific Family Factor (adjusted for age and sex)

Family Factor	Odds ratio	95% C.I.	p value
Family Poverty	2.71	1.02-7.21	0.046
Parents not Caring	2.18	1.01-4.69	0.047
Poor Relationship with Parents	3.01	1.53-5.91	0.001
Often Quarrel with Parents	3.39	2.12-5.42	0.000

**Figure 1.** Odds Ratio of Major Depression for a Given Family Factor in Females. (CI indicates confidence interval)**Figure 2.** Odds Ratio of Major Depression for a Given Family Factor in Males. (CI indicates confidence interval).

DISCUSSION

Depression is known to be more prevalent in high-income countries. In 2013, the mean global prevalence of depression (including dysthymia and major depression) in age 5-17 was 6.2%, with the prevalence in high-income regions being 34.54% in contrast to that in low and middle-income regions of 3.01% (11). In 2013, the lifetime prevalence of major depressive episode in high-income countries was estimated to be 14.6% (12). Our study has found that the prevalence of major depression using PHQ-9 in Macau adolescents is 16.4%. This figure is comparable to the estimate in high-income countries.

This high prevalence of adolescent major depression should raise our awareness. More strategies should be implemented on the prevention and management of the problem. For early diagnosis and intervention, screening for major depression could be carried out in secondary schools. In addition, our prevalence figure is much higher compared to the data in Hong Kong, a place with a similar culture as Macau. A study using the same assessment tool in adolescents in Hong Kong found the prevalence of major depression as 7.6% (10), a figure that is less than half of our finding. This is an interesting finding. Further study would be needed to understand why our higher prevalence of adolescent major depression compared to a nearby city with a similar culture.

The adolescent period is the transition period from childhood to adulthood. Many changes take place, which are likely to have an effect on the adolescent's psychosocial functioning. Even though adolescents strive for autonomy from their parents, parent-adolescent interactions are important in terms of their psychological development and the acquisition of the ability for emotional regulation (13). In fact, family factors have been found to have significant associations with adolescent depression in both western countries and family-oriented culture such as the Chinese culture (14, 15). Our study also looked into the prevalence of 6 family factors and their correlations with major depression in adolescents. We found that "often quarrel with parents" is the family factor that is most significantly correlated with major depression in Macau adolescents. In a cross-sectional study in China, family conflict (Pearson correlation analysis $r=0.38$, $P<0.01$) was found to be significantly correlated with adolescent depression (16). The presence of family conflict was associated with significant risk for suicidal behavior in Chinese adolescents with an OR of 4.94 (17). In addition, the bidirectional relationship between conflict with parents and depressive symptoms was reported in a cohort among Canadian adolescents aged 12-14 years old (18). The study concluded that conflicts with parents can lead to depressive symptoms while being depressed would lead to more conflicts with parents.

Our results are consistent with the above findings even though we assessed quarrel frequency instead of the conflict itself. Conflict is a collective term which means "serious disagreement or argument". In the Chinese studies, studied samples only responded to the literal meaning of family conflict, being asked whether they had family conflict or not. In the Canadian study, conflicts with parents included disagreement and arguments with parents.

In our study, we specifically asked about the frequency of quarrels with parents, which is more objective and accurate in terms of the extent of the conflicts the adolescents had with their parents.

According to the attachment theory, secure attachment in childhood is beneficial to positive developmental outcomes with lower levels of depressive symptoms in later lives (19). Many studies later also suggested a strong link between insecure attachment and the development of depression in adolescents (20). While a higher level of parental warmth has been suggested to relate to better outcomes in adolescents (21), a literature review by Maggie Zgambo and her colleagues has also shown that perceived parental warmth decreases the onset of depression symptoms in children and adolescents (22). Our study looks into adolescents' bonding with their parents in the form of the perceived care from their parents and how the adolescents think about their relationship with their parents. As can be predicted from the attachment theory, in our study, adolescents who think that their parents do not care about them and have poor relationships with their parents were statistically more likely to have major depression. In a longitudinal study involving over 1300 12-20 years old adolescents in the Netherlands, a bidirectional relationship between poor relationships with parents and depression has also been suggested (23). It was shown that perceived relationship quality with both fathers and mothers significantly predicted later depressive symptoms, while adolescents who reported higher levels of depressive symptoms perceived lower quality of relationship with both fathers and mothers one or two years later.

The association between financial strain and depression is well-known in adult (24, 25). Studies in adolescents mainly took family poverty or parental low socio-economic status as adverse life events in childhood and investigated for the long-term association of the childhood adversity with adolescent-onset depression (26, 27). For example, a prospective cohort in Australia has suggested a cumulative effect of family poverty experienced early in life on the later development of depression and anxiety in adolescence and adulthood (28). In another cohort in the United States, childhood poverty is shown to be associated with child-onset depression, adolescent-onset depression and young adult-onset depression with ORs of 2.08 ($P<0.001$), 1.61 ($P<0.05$) and 1.71 ($P<0.05$) respectively. In our study, we looked into the association between major depression and family poverty by monthly salary. Our result has also shown that "family poverty" is associated with an increased risk for major depression with an OR of 2.71. Further analysis by sex suggested that the association occurred only in females. This is consistent with the ROOTS study of the environmental pathways from child adversity to adolescent depression which is observed only in girls (29).

Parental divorce is another childhood adversity that has been widely studied (30, 31). In the WHO world mental health survey 2010, childhood adversity of parental divorce was most prevalent in high-income countries (32). From the study by WHO, 10.1% of the studied adults reported experiencing parental divorce in childhood. This figure is comparable to our findings of 11.4% of the adolescents having experienced parental divorce.

While the experience of parental divorce in childhood is found to be associated with adolescent major depression in one study in Europe (33), our findings did not show association between parental divorce and major depression in the adolescents. This may be due to the strong family bond in Chinese culture. Even after divorce, there is other members from the extended family including grandparents to provide support in the care of the children so that the warmth and care from the family is not greatly affected.

Many studies worldwide have found negative impact of parents' non-standard working hours on children's physical and emotional health (34-37). Yet, few studies investigated the association of adolescent depression with parents' working schedule. We specifically looked into the association of adolescent major depression with parent working on shift because shift work is very common in Macau, considering the reliance on casinos and hotel business. In our study, 40.5% of the adolescents has at least one parent working on shift. In contrary to the findings from other studies, our results did not show any association between having parent needing to work on shift and major depression in the adolescents.

Among all 6 family factors being studied, namely parental divorce, family poverty, not caring parents, poor relationship with parents, often quarrel with parents and parents working on shift, 4 of which were significantly correlated with major depression in Macau adolescents. They are family poverty, not caring parents, poor relationship with parents and often quarrel with parents. From the results, we understand that good relationship in the family is more important than a complete family structure in terms of the correlation with major depression in Macau adolescents. We mean the usual structure of having both parents in the family with complete family structure. In our study, the adolescents not with a complete family structure most of the time, i.e. the ones who had parents needing to work on shift or whose parents have divorced, were not with increased risk for major depression. While the increased risk for major depression were seen in the adolescent who perceived their parents to be not caring, who had poor relationship with their parents and who often quarrel with their parents. These results have inferred the importance of promoting parenting skills and encouraging communication within the family to prevent adolescent depression. Considering the increasing risk of major depression in adolescents with family poverty, more work may have to be done to help the low-income families. Emotional support to the children in the family is important in addition to financial subsidies.

There are several limitations of our study. Firstly, all of our assessments are subjective measures or self-report by the adolescents, they may have deviated from the real condition. Self-report method was used in the survey which we extracted the data for convenient collection of the data. For most family factors, it is not easy to have an objective assessment. However future studies should consider to include parents' information instead of relying only on the adolescents' report. More detailed assessment of parent-adolescent relationship should also be conducted using the validated assessment tool. Secondly, the survey was conducted on school days, if the adolescents who were absent thus did not fill in the survey were absent due to severe major depression, the result may be underestimate of the real situation.

Finally, our study is a cross-sectional study that only showed correlations, prospective studies are needed to establish the cause and effect relationship of the family factors with adolescent major depression.

CONCLUSION

Our study is the first study in Macau that assessed the prevalence of major depression in Macau adolescents and the correlation between adolescent major depression and different family factors. We have found a high prevalence of major depression in Macau adolescents which is comparable to that in high-income countries and strikingly with a figure which is two times that in a nearby city with a similar culture.

Our findings have shown that having poor relationship with parents, with parents not caring, often quarrel with parents and having experienced family poverty are associated with significant risk for major depression, with 2-3 times increased risk compared to adolescents without the problems. There is higher prevalence of major depression in adolescent females and major depression in adolescent females is associated with more family factors. "Often quarrel with parents" is the only factor that is associated with major depression in both males and females.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

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Ileosigmoid knotting: Case report and literature review

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ABSTRACT

Objective: Ileosigmoid knotting (ISK) is the wrapping of the ileum around the sigmoid colon and its mesentery or vice-versa. ISK is a rare cause of bowel obstruction in general and rare during pregnancy.

Case: We present a case of ISK, a Pregnant lady 29th weeks gestation, which was treated successfully in our institution – Khoula Hospital – Muscat - Sultanate of Oman.

Keywords: Ileosigmoid, knotting, pregnancy

INTRODUCTION

Ileosigmoid knotting (ISK) is the wrapping of the ileum around the sigmoid colon and its mesentery or vice-versa (1).

ISK is a rare cause of bowel obstruction in general, and a rare diagnosis during pregnancy. ISK Diagnosis is very difficult preoperatively due to the condition's rarity, the difficult clinical assessment during pregnancy and its atypical radiographic features. Exploration laparotomy uses to reach the final diagnosis and manage refractory bowel obstruction with or without peritonitis. Most cases manage by resection with stoma apart from a few cases handled without a stoma.

To our knowledge, this is the First ISK case to be published from Oman.

CASE

Thirty-two years old woman, primigravida at 29 weeks of pregnancy presented to the obstetric emergency room in our institution with history of generalized abdominal pain associated with nausea and repeated vomiting with absolute constipation lasting for a day. She had no vaginal bleeding or discharge and no significant past medical or surgical history.

Initial examination at the time of presentation: The patient was alert, conscious and oriented, blood pressure was 110/70 mmHg, heart rate 74 beats/minute, afebrile.

The abdomen was soft, cervix posterior os closed, and ultrasound showed a breech alive fetus.

Laboratory investigations at presentation were within normal levels.

Patient was deemed to in preterm labour pain, hence was admitted overnight for observation.

Upon follow up next day, the patient had repeated episodes of vomiting. Abdominal pain markedly increased in intensity. Her heart rate increased to 140 beats /minute, Maintaining her blood pressure, the temperature of 37.7 °C.

Abdominal examination revealed marked distension, generalized tenderness with guarding and rigidity, Absent Bowel sounds. Digital rectal examination (DRE) showed an empty ballooned rectum.

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Laboratory investigations repeated and showed marked leukocytosis (from $10.12 \times 10^3/\text{uL}$ to $24 \times 10^3/\text{uL}$).

Radiological investigations:

- Plain lower chest and abdominal X-rays showed dilated large bowel loop with coffee bean sign and no free gas under the diaphragm.

- Contrast-enhanced CT scan of the abdomen and pelvis showed a significant amount of free fluid involving all peritoneal cavities. Markedly dilated small bowel loop noted at the left hypochondria and showing air-fluid level with decreased wall enhancement and pneumatosis with fecalization. Superior mesenteric vessels were seen stretched and swirled in the left para duodenal space.

The large bowel appeared normal diameter and showed normal wall enhancement. Pneumoperitoneum not defined. Gravid uterus showed with a single fetus.

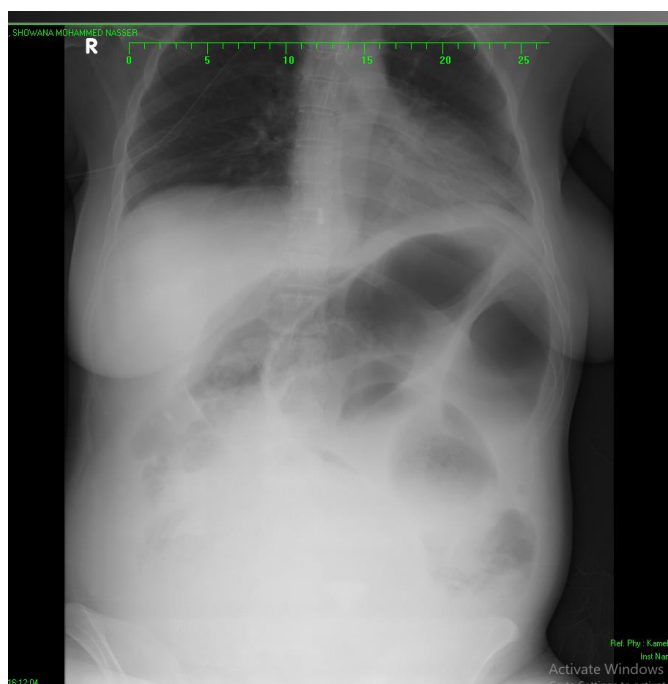


Figure 1: Plain abdominal x-ray – supine position.

After proper resuscitation, the decision was made to take the patient for exploration laparotomy. Consent was taken for a simultaneous caesarean section as the baby was the breech presentation, and the mother is primigravida. For most cases caesarean will be required in case of premature delivery after surgery (which has high probability)

Exploration of the abdominal cavity was done.

Intraoperative Findings: After 150 cm from DJ flexure, all rest of bowel is gangrenous till 10 cm from the ileocecal valve.

The entire gangrenous segment is twisted around its mesentery surrounding a dilated gangrenous sigmoid volvulus. Abdominal cavity had full of serosanguinous fluid.



Figure 2: Intra operative picture showing the Ileosigmoid knot

CS was done by the obstetric team delivering the alive male baby.

Resection of all the gangrenous segments of the small bowel was operated, with end-to-end hand-sewn anastomosis. Then resection of the sigmoid colon was done, side to side colo-rectal anastomosis was done using linear cutter stapler.

Postoperatively, the patient was shifted intubated and ventilated to ICU, in septic shock.

Gradually patient recovered, was extubated in the 9th post-op day, passed a motion in the 11th post-op day and shifted out of ICU in the same day, discharged home at the 15th post-op day in good general condition after returning to normal feeding and bowel motion habits. The delivered baby was intubated for one day, admitted to SCBU, discharged from the hospital in good condition after 34 days.

The patient was followed up in the OPD clinic for five weeks post-operative, and she was doing well, has no complaints, tolerating a normal diet and passing motion normally.

DISCUSSION

The Ileosigmoid knot was first described in 1845. It is common in Africa, Asia and Middle East. Males are more commonly affected than females (4:1), usually around the age of 40 years (range 4-90 years). ISK in pregnancy is a rare condition. There are only 9 reported cases of ISK in pregnancy in the literature between 1967 and 2009; with the incidence of ISK in pregnancy ranging from 3.2% to 5.9% of all ISK cases and 12.5% to 36.4% of ISK cases in female patients (2).

Pathophysiology of ISK is not fully understood, but it is being hypothesized that Loops of the small bowel may twist around its mesentery then by progressive peristalsis, this closed-loop wrap around sigmoid volvulus.(2) There are secondary factors besides the anatomical factors mentioned above, such as late pregnancy, trans-mesenteric herniation, Meckel diverticulitis with the band, and ileocecal intussusceptions (3).

Type I	The ileum (active component) wraps itself around the sigmoid colon (passive component) in a clockwise or anticlockwise direction.	(Type A when clockwise and type B when anticlockwise).
Type II	The sigmoid colon (active component) wraps itself around a loop of ileum (passive component) in a clockwise or anticlockwise direction.	
Type III	The ileocecal segment (active component) wraps itself around the sigmoid colon (passive component).	

Notes: Reproduced from Alver O, Oren D, Tireli M, Kayabaşı B, Akdemir D. Ileosigmoid knotting in Turkey. Review of 68 cases. *Dis Colon Rectum*. 36(12):1139–1147. <https://doi.org/10.1007/BF02052263>⁶

The predominant symptoms and signs of presentation include abdominal pain and tenderness (100%), abdominal distension (94% to 100%), nausea and vomiting (87% to 100%), rebound tenderness (69%), and shock (0% to 60%) (2, 5, 6, 7).

Upon review of literature, we found very few reported cases in the English language describing ISK. Multiple factors made our case different than other cases, i.e. simultaneous caesarean section was done delivering alive male baby 29 weeks gestational age. That decision was taken because the presentation was breech. “We found that non-obstetric surgery during pregnancy was associated with a higher risk of adverse birth outcomes. We estimated that every 287 surgical operations were associated with 1 additional stillbirth, every 31 operations associated with 1 additional preterm delivery, every 39 operations associated with 1 additional low birth weight baby, every 25 operations associated with 1 additional caesarean section, and every 50 operations associated with 1 additional long inpatient stay” (8).

The risk that a breech baby will need caesarean section in a primigravida mother is 62% (9).

So our decision was clear from the beginning to perform both surgeries in one session.

We have noticed a contradiction between reporting well-enhanced non dilated large bowel while we found that the sigmoid colon was dilated and gangrenous mandating resection, hence surgical teams should be cautious in correlating radiological findings and having a high index of suspecting bowel ischemia in similar scenarios.

Another unique feature in our case management is that resection for both small bowel and sigmoid colon done, with direct single-stage anastomosis was done after proper on table lavage. By doing this, we are following the recommendations of all recent textbooks and studies in general surgery, which offered a better quality of life and reduced surgical morbidity.

Author Contributions: AAH, ARA, KA, FA, HME, YA: Study design, Patients examination, Surgical operation Literature review, Data collection and/or processing, Analysis and/or interpretation, ARA: Article Writing, Revision

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

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Segmental cystic dilatation of the ureter in a Sudanese adult. A case report

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ABSTRACT

Objective: Segmental cystic dilatation of the ureter is extremely rare in adults. This article presents a case of segmental cystic dilatation of the left ureter with proximal dilated upper left ureter and ipsilateral atrophied kidney, while the distal ureter with normal calibration.

Case: Excision of the cyst with proximal ureter and kidney was done. Segmental cystic dilatation of the ureter should be considered in the differential diagnosis of intra-abdominal cystic mass.

Keywords: Megaureter, Segmental megaureter, Segmental cystic dilatation, Adult

INTRODUCTION

Congenital anomalies of the kidneys and urinary tract represents abroad range of disorders which result from abnormalities in the development of the urinary collecting system, abnormal embryonic migration of the kidney, and abnormal renal parenchymal development (1). Megaureter is defined as the presence of an enlarged ureter with or without concomitant dilatation of the upper collecting system. The normal diameter of the ureter is 3 mm and in practice ureter of 7 mm and more is considered a megaureter (2). Megaureters are categorized as primary and secondary megaureters. Primary megaureter is related to those with idiopathic congenital alteration of the vesicoureteral junction. The primary megaureter is categorised into obstructed, refluxing, and non-refluxing non-obstructing types. Secondary megaureter is due to distal obstruction in the urethra, bladder, or distal ureter (3). However, segmental megaureter or segmental cystic dilatation of the ureter is a very rare entity, and only a few cases were reported in the literature (4, 5, 6, 7, 8, 9, 10, 11). This paper will present a case with segmental cystic dilatation of the ureter with dilated proximal upper ureter and atrophied ipsilateral kidney.

CASE

Thirty-Seven years old male presented to us in Ribat university hospital, Sudan, in September 2017 with slowly progressive abdominal swelling over two years period until it reached its maximum size and occupied the entire abdomen. The swelling was associated with dyspeptic symptoms and burning micturition. No loss of weight or loss of appetite. No abdominal pain, vomiting, jaundice, or change in bowel habits. The patient is not known as diabetic, hypertensive, or had a chronic illness. His past medical history was unremarkable. No family history of similar condition or malignancy. The patient is not a smoker or alcohol consumer.

On examination, the patient was well, not pale or jaundiced. He was on good nutritional and performance status. Abdomen was distended all over with full flanks, and the umbilicus was flat. Scar, visible pulsation, peristalsis, or dilated veins have not been observed. Hernial orifices were intact. There were a pelvi-abdominal mass about 35*25 cm, which firm, smooth, immobile, dull to percussion with positive fluid thrill. Systemic examination was normal. CT abdomen with oral and I.V. contrast was showed, large pelvi-abdominal cystic mass containing fluid with thin and smooth regular wall. No calcification, septation, or intra-lesion complex mass. The cyst was displacing the bowel to both sides of the abdomen with no feature of obstruction.

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The right kidney was normal. The left kidney was atrophied and not taking the contrast. No other abnormality. Possible differential diagnoses were mesenteric cyst and pancreatic pseudo-cyst.

Pre-operative workup included blood investigation, urine analysis, and cardio-respiratory assessment and all were unremarkable.

Exploration revealed a large retroperitoneal cystic mass about 35*25 cm and had been found to continue distally with normal caliber left ureter and proximally with dilated left upper ureter ipsilateral atrophied left kidney. A urologist was consulted and involved in the surgery. The consent was taken for removal of the left kidney and ureter. The cyst was removed along with the dilated upper ureter and kidney after ligation and division of the left renal pedicle and left gonadal vessels. The normal distal ureter was ligated and left in situ. The cyst was occupying the left mid-ureter.

The kidney, ureter, and cyst weigh 7.7 kg. The cyst size was 34*23.5*7 cm with thin walls containing hemorrhagic fluid. The attached left kidney and cystically dilated upper ureter measure was 27*5*2 cm. the cut surface of the kidney showed a multi-locular cyst and no renal tissue was identified (figure 1).



Figure 1: Ureteric cyst with proximal dilated ureter and atrophied kidney (K).

Microscopically, the cyst showed a thin fibrous wall lined with partially attenuated epithelium. The attached kidney showed cystic spaces lined with urothelium replacing renal parenchyma. And the ureter was lined by hyperplastic urothelium. No evidence of malignancy in the specimen.

The postoperative course was uneventful. No postoperative complications from the surgery or anaesthesia. Follow up in outpatient clinic to assess the function of remaining kidney, no raise in renal functions or any abnormality seen. The patient is in good health and on follow-up every 6 months with renal function test and abdominal ultrasound.

DISCUSSION

Few cases of segmental megaureter and segmental cystic dilatation were reported in the literature and most of them were in children. In 1986, Mandell et al reported 4 cases of congenital megacalycosis associated with ipsilateral segmental megaureter in children. Of their cases, the megaureter is due to narrowed a peristaltic ureter (4). In 1995, Ramaswamy reported one pediatric patient with segmental megaureter with sparing of proximal and distal ureter (5). A similar case was reported in 2010 by Karman et al in two months old infant with segmental ureteral dilatation with sparing of proximal and distal ureter (6). In 1997, Pinter et al reported a case with bilateral segmental megaureter (7). Soler et al. reported a case of multi-cystic dysplastic kidney and contralateral megacalycosis associated with ipsilateral distal segmental megaureter, in 2004 from Spain (8). In 2007, Prieto et al reported a case of congenital severe mid-ureteral dilatation associated with mild proximal ureteral dilatation and normal calibre of distal ureter similar to our case (9). In 2015, Dutta and Harsh reported a 7 years old male child with segmental megaureter and ipsilateral megacalycosis and contralateral vesico-ureteric reflux. Cystoscopy of this child revealed an absence of ipsilateral ureteric meatus and golf hole opening of refluxing ureter. The ureter distal to dilated part is of normal calibre but opened in the bladder neck (10).

We found only 2 cases of congenital segmental megaureter in adults associated with urolithiasis in the literature, which Rosenblatt et al. reported in 2009. The first one (58 years old) had a 2.3 cm stone in a dilated segment of his left distal ureter with normal-sized proximal ureter and mild dilatation of ipsilateral collecting system. The other case is 48 years old with dilated left distal ureter with ipsilateral 9 mm renal stone (11).

Several theories have been speculated regarding the pathophysiology of congenital segmental megaureters. Ramaswamy suggests that the segmental megaureter was a variant of non-refluxing megaureter and attenuated nexuses and thin myofilaments might be responsible for this entity, as their case (5). In another study, it was suggested that aganglionosis of the distal segment of the ureter resulted in dilatation of the proximal segment as in cases of achalasia and Hirschsprung's disease (4). Pinter suggests that recanalization of solid ureteral duct, if abnormal, might produce segmental megaureter (7).

The current belief is that primary obstructive megaureter is present primarily in adults when the congenital abnormality does not cause symptoms or illness and is not seen via an imaging study performed during childhood.

Spontaneous regression fails to occur, yet patients remain asymptomatic during childhood. Eventual symptoms include urinary tract infection, renal parenchymal disease, and recurrent stone formation (10).

Treatment of segmental cystic dilatation of the ureter should be tailored according to ipsilateral kidney function and the length of the segment involved (6). If the residual length of the proximal and distal ureteral segment is enough with good ipsilateral kidney function, end to end uretero-ureterostomy after excision of the cyst can be performed. If excision is not possible, tailoring or trimming of the dilated segment should be considered. If the ipsilateral uretero-renal function is poor, hypoplastic, or dysplastic, a nephroureterectomy is advised, as in our case.

CONCLUSION

Segmental cystic dilatation of the ureter should be distinguished from ureterocele and other conditions such as ureteral diverticulum. At the same time, patient should be investigated for possible associated urinary tract system anomalies such as megacalycosis, duplication of the collecting system, and hypoplastic, dysplastic, or non-functioning kidney (6).

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

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Erythromycin versus Azithromycin: which is the fittest substitute for Penicillin in allergic patients?

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ABSTRACT

Objective: Since the usage of Penicillin in the early 20th century, limitations to its use such as allergy, began to demand alternatives, cause of life-threatening adverse reactions of Penicillin. Plus, the difficulty and cost to establish patient's allergic profile and the discrepancy between test results and medical history add to this problem. In order to find a perfect substitute for Penicillin, many articles have reported the successful use of drugs of the macrolide class in treating infections for which Penicillin would normally be indicated as the first line but cannot be used due to allergy. Compiling recent publications, we compared Erythromycin and Azithromycin, as the most prominent macrolide agents which considering efficient against for broad range microbial spectrum beside determine which is the fittest to substitute Penicillin in allergic patients. We were compelled to conclude that although the drugs are fundamentally similar, Azithromycin not only presents better adverse reaction profile, but has proven to be superior in efficacy to Erythromycin in many infections where the substitute is needed, and also widens its appliance against to atypical infections, which are subject of promising for the further investigations.

Keywords: Penicillin; Macrolides; Hypersensitivity; Azithromycin; Complementary Therapies, Erythromycin

INTRODUCTION

Penicillin is a β -lactam antibiotic widely studied and one of the oldest antimicrobial drug known to science, since its introduction by Alexander Fleming in 1928 (1). Almost a century from its discovery, Penicillin have been throughout used worldwide and modified in order to improve its therapeutic results and overcome growing microbial resistance (2), and even though many other antibiotics were introduced to the scientific community, Penicillin is still the preferred drug to treat many infections (3).

Although considered a safe drug, many patients report adverse reactions to Penicillin, which limit their use, the most important one being allergy. Approximately 10% of US population has reported allergies to β -lactam agent penicillin, which range in presentation hazard from low-risk cutaneous rashes to anaphylaxis, despite the fact that those reactions are clinically considered uncommon, they configure emergencies that deserve importance (4).

It is reported that hypersensitivity to Penicillin - IgE mediated or not - waves over time, and it is stated that 90% of patients labelled as "penicillin allergic" are able to tolerate its use given specific treatments (5). Cross-reactivity between Penicillin and other β -lactams are also less common than previously speculated, which should undermine the importance of figuring out a substitute for Penicillin, but the acute reactions continue to be an important clinical problem (6), mainly considering that in spite of being reasonably viable to identify the risk for a serious response such as anaphylaxis through immunodiagnostic techniques, patients affected by acute systemic or complicated infections would not be able to undergo penicillin desensitization processes.

Another important consideration, especially in low and average-income countries, is the cost of penicillin allergy evaluation, which seems to be considerably high (7). Not only should it be costly to assess allergy in such populations, but it would also be challenging to follow-up on the results of diagnostic tools, such as the skin test for sensitivity.

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The most well-established alternative treatment for infections for which Penicillin would be the first choice is usually using macrolides agents, notably Azithromycin and Erythromycin (3) (8) (9) (10). Thus considering that finding a suitable substitute for penicillin antibiotic therapy is necessary, it is the aim of this review to compare the two alternative drugs in terms of efficacy, spectrum, compared effectiveness and safety profile, in order to find the optimal substitute among them.

MATERIAL and METHODS

The present review focused research on well-oriented clinical trials and reviews concerning comparisons between Erythromycin and Azithromycin, given penicillin allergy as the main reason to figure its optimal substitute.

Article research was conducted on PubMed, Scielo, Science Direct and Medline bases. The following keywords were used: "allergy", "penicillin", "management", "azithromycin", "erythromycin", "macrolides", "management", "adverse reactions", "clinical trials", "antibiotic" as well as its equivalents in Portuguese. Boxes "AND" and "OR" were selected when they were present.

We also recurred to the latest editions of pharmacology textbooks in order to report more fundamental subjects, which would not find place within research articles, all which are referred to accordingly.

Enters and records identified in the electronic data banks were exported to the platform Rayaan, used in selection. Studies were initially filtered by title and abstract independently and those selected on a first filtration were evaluated regarding eligibility and inclusion in this review by full-text analysis.

Articles of opinion and isolated case reports were the only automatic exclusion criteria for article analysis, and no case complications were considered as to differ among infection presentations. Articles were also not excluded based on language, date or place of conduction.

RESULTS

1. Macrolides: An heterogeneous class

Erythromycin, Azithromycin and clarithromycin are the three classical constituents of the macrolide class of drugs. Erythromycin was the first to be introduced and although Azithromycin and clarithromycin were then presented due to several distinct advantages over the former, they all function in a similar way, by inhibiting protein synthesis in susceptible organisms by binding to the 50S ribosomal subunit (11).

However, it is important to note that Erythromycin does not inhibit the protein binding but a translocation step in which a peptidyl-tRNA moves from the acceptor locus over the ribosome to the peptidyl donor locus (12).

Despite the same mechanism of action, focusing in the Azithromycin and Erythromycin comparison, the first articles published investigating newer macrolide's contributions to the class reported great pharmacokinetic results. Those included improved oral bioavailability, longer half-life, higher tissue concentrations and fewer gastrointestinal adverse effects (13).

2. Differences in antimicrobial spectrum in common infections

As we have presented, macrolides were introduced in order to serve as a substitute for Penicillin, among other purposes. One good reason to have a safe alternative to Penicillin is the cost of its allergy tracking, which is fairly high even with the latest tests, costing around US\$540 (14), and is often a great offset to middle-income country patients.

The spectrum of Erythromycin was developed in order to ideally cover all Penicillin covered microorganisms. As Azithromycin was only introduced later, enhancements can be observed concerning their antimicrobial spectrum as we shall see individually compared.

2.1 Respiratory tract infections

Famous pharmacology textbook Goodman & Gilman latest edition compiles updated article records concerning their spectrum (15). Erythromycin is appropriated to treat several respiratory tract infections, the most common etiological agents being *S. pneumoniae*, *H. influenzae* and also *M. catharralis*. In fact, all macrolides are fit to treat those infections, and are usually the most prescribed after penicillin agents, such as Amoxicillin. When it comes to atypical respiratory infections, such as pneumonia caused by *M. pneumoniae* and *C. pneumoniae*, all macrolides are fit to prescription, together with quinolones and tetracyclines.

The only relevant discrepancy found in efficiency that is also well-documented is in *Legionella* infections treatment, where Azithromycin is usually preferred due to excellent in vitro activity, higher tissue availability, single daily dose and better tolerability (16). In fact, Azithromycin seemed to have taken a great preferability, since most of the recent literatures actually compare its efficiency to other drugs, whereas Erythromycin is not cited, although also efficient (17).

2.2 Cutaneous and soft tissue infections

Macrolides are a suitable alternative to Penicillin treating cutaneous and soft tissue infections.

In acneic infections, Erythromycin is rarely used due to immense bacterial resistance developed since the 80's, and Azithromycin is the preferred drug, although it has also seen minor increase of resistance recently (18).

Common resistance to macrolides is observed in *Staphylococcus cutaneous* infections, where neither Azithromycin nor Erythromycin is recommended in Penicillin resistant or sensible strains as an immediate alternative (19).

Azithromycin's overall superiority to its counterpart macrolide in these infections have lead researchers to experiment their potential to cure skin infectious conditions even on complicated and atypical cases. It was added to post-cesarean infection antibiotic-prophylaxis treatment and is has been shown to reduce its incidence, although it did not seem to reduce wound complications (20). Several trials have shown Azithromycin is as effective as Penicillin in treating early syphilis acute cutaneous manifestations (21) and also have great records in treating cutaneous Leishmaniasis (*Leishmania amazonensis*) when added to N-methyl glucamine therapy compared to glucamine alone (22). It's also considered to maintain similar effectiveness and adverse reaction profile in treating cutaneous lyme borreliosis to doxycycline, cefuroxime axetil, ceftriaxone, amoxicillin, penicillin V, and minocycline (23).

2.3 Erysipelas and cellulitis

Erysipelas and cellulitis management poses great challenges by itself, even concerning the first-line antibiotic therapies, due to *Streptococcus* and penicillin-resistant *Staphylococcus* association (24). The acute hypodermic infection of erysipelas, usually also concomitant with some form of cellulitis, is mainly caused by a group A beta-hemolytic *Streptococcus*, which should make macrolides a fit choice (25).

Clinical trials showed that azithromycin and Erythromycin present similar effectiveness in treating cellulitis and erysipelas in comparison to beta-lactams and lincosamides, with an overall better cure ratio and better adverse reaction profile - a major parameter considering their use as beta-lactam substitute (26). However, prophylactic use of Erythromycin has shown several adverse reactions in comparison to beta-lactams, which lead to discontinuation of treatment in another study concerning cellulitis and erysipelas (27). Azithromycin, nevertheless, seemed flawless, and it also very successfully recorded as therapeutic agent on cellulitis even on immunocompromised patients (28).

2.4 Chlamydia infections

All macrolides are suitable to treat chlamydia. Authors usually cite that their effectiveness are so similar in chlamydia infections that the choice is mainly among their differences in pharmacokinetics (29) (30).

In this scenario, Azithromycin is preferred due to better adverse reaction profile (31), but a shift can be observed in recent literature concerning the very choice for macrolides. High rates of recurrent and persistent chlamydia in women after azithromycin treatment rose the demand for a better drug (32) and this endeavour have found a breakthrough that will probably keep macrolides on the shelves for the near future: doxycycline. Doxycycline have aced the treatment for the many presentations of chlamydia infections, highly exceeding Azithromycin's success (33) (34).

CONCLUSION

In summary, considering the evidence compiled in recent literature, the authors are compelled to state that macrolides are safe and have great effectiveness in substituting Penicillin in allergic patients. Comparing macrolide drugs, as similar as Erythromycin and Azithromycin might be the latter overall antimicrobial attributes is highly superior.

Not only Azithromycin showed sufficient capability of substituting Penicillin in diseases where it was the first line drug, but also surpasses its effectiveness in cases such as respiratory tract infections, and also widens macrolide application potential, as it is being experimented on different diseases previously treated else-wise, like Leishmaniosis. Also considering macrolides safety and adverse effects profile, Azithromycin has been found to always overcome deficiencies and adverse reactions present on erythromycin treatment, which usually leads to discontinued therapy.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

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Various substitutes of brachytherapy boost after neoadjuvant chemoradiation for locally advanced cervical cancer. Literature Review

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ABSTRACT

Objective: Concurrent chemoradiotherapy (CCRT) is widely regarded as the gold standard for locally advanced cervical cancer (LACC). Radio Therapy encompasses pelvic external beam radiation therapy (EBRT), followed by intracavitary brachy therapy (BT) to boost the cervix. However, in developing countries, there is a tendency to prefer surgery over other types of treatments for several reasons - surgery is easily obtainable, more acceptable, and understandable culturally. On the other hand, in developed countries, The utilization of brachy therapy (BT) to boost the cervix in patients with Cervical Cancer (CC) has been gradually declined because of the advent of sophisticated techniques for EBRT. Recently, the treatment of LACC has been a point of controversy. We have no prospective data to justify that surgery or modern EBRT can be used in place of intracavitary BT boost in women with locally advanced CC. This study aims to review existing information about brachytherapy alternatives after neoadjuvant chemoradiation.

Material and Methods: An electronic search of the PubMed database was conducted to obtain key cervical cancer literature. The MEDLINE/PubMED (www.ncbi.nlm.nih.gov) database was chosen as it remains the most widely used resource for medical literature. Additional records were searched in other resources.

Results: The first phase of screening identified 18 articles for the first search term ("Adjuvant hysterectomy" AND "Cervical Cancer"), 10 article for the second search term ("IMRT boost" AND Cervical cancer") and 11 articles for the third search term ("SBRT" AND "Cervical Cancer"). In sum 39 articles were identified to be relevant for the second phase of screening. Studies that included less than five patients with investigated intervention or did not provided enough information about at least one primary endpoint were excluded. A total of 20 (11-adjuvant hysterectomy, 4-IMRT boost, 5-SBRT boost) papers met the selection criteria and were found eligible for this review.

Conclusion: When all these alternative approaches to ICB are evaluated, adjuvant hysterectomy appears to have treatment outcomes comparable to standard of care, while SBRT appears to have only modest yearly results. As a result, the majority of writers believe that neoadjuvant chemoradiation followed by radical surgery or SBRT may be a realistic therapeutic option for patients with LACC, not merely when ICB is unavailable, technically impractical, or rejected. Large, randomized-controlled trials are required to conclusively demonstrate or invalidate non-ICB alternatives for cervical cancer treatment.

Keywords: Cervical Cancer, Adjuvant hysterectomy, IMRT Boost, SBRT boost, Brachytherapy boost.

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INTRODUCTION

Until the early nineteenth century, cervical cancer (CC) therapy was limited to surgery. People thought that the entire site of the disease had to be excised. The need for a very aggressive radical surgery had been mostly emphasized in locally-advanced cervical cancers (LACC) patients (1).

Marie and Pierre Curie's discovery in 1898 was the game changer point. One of the first published claims to the use of radium was that of Margaret A. Cleaves (1848 - 1917) of New York. She treated a patient with LACC with sealed glass tubes of radium through the vagina. In the 1910s, the American surgeon Robert Abbe (1851–1928) made a vaginal applicator for CC (2). As time passed, radiation therapy (RT) became a respectful part of CC therapy, and soon after, all patients with LACC, regardless of age or operability, were assigned for primary irradiation.

Based on a series of GOG (Gynecologic Oncology Group) clinical research findings that published in 1999 National Cancer Institute (NCI) was issued a notice which suggesting RT in conjunction with concurrent chemotherapy instead to RT alone for patients with a variety of clinical situations (for both locally progressed and post-radical hysterectomy patients). As a result of a randomized research demonstrating its lack of benefit over survival, adjuvant extra-facial hysterectomy has been steadily phased out for bulky or 'barrel' shaped cervical cancers. Patients with early-stage cervical cancer are regarded to be the ideal candidates for surgery, while LACC surgery is accepted only for salvage treatment. Even though it is known that optimal chemoradiation therapy is unable to sterilize pelvic lymph nodes in around 16% of cases which may suggest a therapeutic role for adjuvant hysterectomy, systematic pelvic lymph node dissection became a diagnostic/prognostic procedure, and its therapeutic potential has been reported only in metastatic bulky lymph nodes (3-5).

Nowadays, Concurrent chemoradiotherapy (CCRT) is widely regarded as the gold standard for LACC. RT encompasses pelvic external beam radiation therapy (EBRT), proceeded by intracavitary brachy therapy (BT) boost to the cervix (6). However, in developing countries, there is a tendency to prefer surgery over other types of treatments for several reasons - surgery is easily obtainable, more acceptable, and understandable culturally. On the other hand, in developed countries, the utilization of BT to boost the cervix in patients with CC has been gradually declined because of the advent of sophisticated techniques for EBRT. Recently, the treatment of LACC has been a point of controversy. We have no prospective data to justify that surgery or modern EBRT can be used in place of intracavitary BT boost in women with locally advanced CC. This study aims to review existing information about brachytherapy alternatives after neoadjuvant chemoradiation.

MATERIAL and METHODS

An electronic search of the PubMed database was conducted to obtain key literature for cervical cancers. The MEDLINE/PubMED (www.ncbi.nlm.nih.gov) database was chosen as it remains the most widely used resource for medical literature. Additional records were searched in other resources – EMBASE (www.embase.com), Cochrane Central Register of Controlled Trials (CENTRAL) (www.thecochranelibrary.com),

Google Scholar (scholar.google.com/), CINAHL (www.ebscohost.com), APA (www.apa.org/pubs/databases), Opengrey (<http://www.opengrey.eu/>); Z-library (<https://z-lib.org/>); Books; The same search strategies was used for all databases. The following search terms were used: “Cervical Cancer”, “Adjuvant hysterectomy”, “IMRT Boost”, “SBRT”.

Inclusion criterias:

- I. Studies that included patients with intact locally advanced cervical cancer (> FIGO IB2)
- II. Studies that included patients with nonmetastatic cervical cancer
- III. Studies that included patients treated with Linac
- IV. Studies that included more than 5 patients with investigated intervention
- V. Studies that provided at least one primary endpoint, including local control (LC), overall survival (OS), or grade ≥ 3 toxicity

Exclusion Criterias:

- I. Studies that included patients with recurrent cervical cancer
- II. Studies that included patients with metastatic cervical cancer
- III. Studies that included patients treated with Cyber knife or Tomotherapy
- IV. Studies that included less than 5 patients with investigated intervention
- V. Studies that provided no primary endpoint, including local control (LC), overall survival (OS), or grade ≥ 3 toxicity
- VI. Studies that included patients with only FIGO IB stage group cervical cancer
- VII. Case reports, review articles and editorials.

Human studies published in English were used to narrow down the search results. Duplicate studies were deleted from the studies collected from the databases for each search phrase. Following the first screening of abstracts, full-text publications were evaluated for eligibility in the second screening step. The studies were screened individually for each search term

RESULTS

Applying the predefined inclusion criteria, the first phase of screening identified 18 articles for the first search term (“Adjuvant hysterectomy” AND “Cervical Cancer”), 10 article for the second search term (“IMRT boost” AND Cervical cancer”) and 11 articles for the third search term (“SBRT” AND “Cervical Cancer”). In sum 39 articles were identified to be relevant for the second phase of screening.

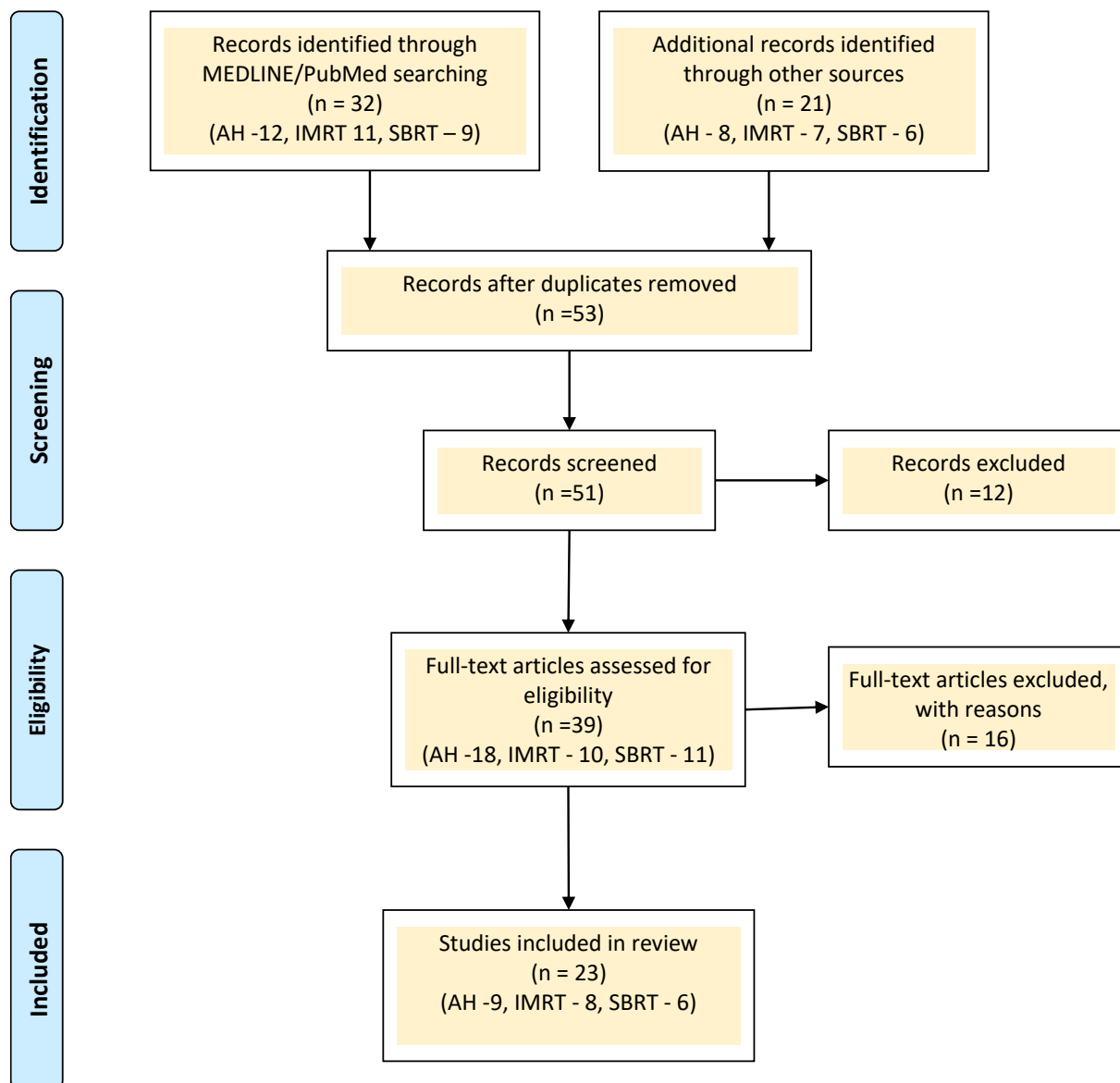


Figure 1. Identification of studies via databases and registers

During the second phase of screening, the full texts of each article were analysed individually. Studies that included less than five patients with investigated intervention or did not provide enough information about at least one primary endpoint were excluded. A total of 20 (11-adjuvant hysterectomy, 4-IMRT boost, 5-SBRT boost) papers met the selection criteria and were found eligible for this review (Fig.1).

Adjuvant hysterectomy

The University of Texas M. D. Anderson Cancer Center first introduced postirradiation hysterectomy to improve the primary lesion's cure rate; however, some patients were also chosen for pretreatment laparotomy and node dissection to improve the cure rate in patients with nodal metastasis. Series of reports were published by the MD Anderson Cancer Center in the 1970s, since then, the role of adjuvant postirradiation extra fascial hysterectomy has been a source of controversy.

The available data have defined neither the potential role post-irradiation hysterectomy nor the extent of radicality that this procedure should require to maximize the outcomes without increasing the level of morbidity. A few authors reported disappointing results related to the high rate of surgical complications while applying hysterectomies after the entire course of chemoradiation, consisting of EBRT combined with chemotherapy followed by intracavitary brachytherapy (7-8).

Previously in 2007, Ferrardina (9) and colleagues demonstrated that neoadjuvant chemoradiotherapy followed by hysterectomy resulted in a high proportion of full pathological response and an acceptable rate of DFS and OS. Furthermore, a low % age of intra- and post-operative complications was observed. This was the first prospective clinical trial to exclude brachytherapy as a part of treatment.

The authors of this study overlooked the adjuvant hysterectomy (AH) conception in favor of a multimodal strategy that included chemoradiation and radical hysterectomy (RH). Patients who included in the study were FIGO stage IB2-IVA. Results could be criticized as we cannot see outcomes separately for the different stage groups and makes an impression as results could be improved identical for all stage groups.

Shortly thereafter, Francesco Fanfani and colleagues published another study from Italy. The research enrolled 39 patients with stage IIIB CC as defined by the International Federation of Gynecology (FIGO). Patients were treated with whole pelvic irradiation (range, 39.6-50.4 Gy) combined with cisplatin and 5-FU. Between 6 and 8 weeks after the end of neoadjuvant CTRT, patients who responded clinically got a RH. In conclusion, the authors noted that chemoradiation followed by RH may be feasible in patients with stage IIIB cervical cancers with a low rate of complications and a survival outcome comparable to that of chemoradiotherapy, allowing for assessment of pathological response and its impact on clinical outcomes (10).

In 2010, Ferrardina and colleagues published updated paper with a median follow up of 58 months (28 months in the previous report) where 3- and 5-years OS and DFS were still awe-inspiring while consequences resulting from multimodality treatment were reported to be acceptable. According to observations, radical surgery was related with a reduced risk of local recurrence than extra fascial hysterectomy or no surgery. Patients with a large residual tumor who had completion-surgery had a better prognosis. Surprisingly, clinical outcomes were quite encouraging with 5-year DFS and OS of 75% and 70%, respectively; moreover, in stage III-IVA patients, 5-year DFS and OS of 58% and 62% was reported (11). In their next phase II clinical trial (12), published in International Journal of radiation Oncology in 2014, Ferrandina and colleagues aimed to evaluate the efficacy of accelerated fractionation radiation therapy by concomitant boost associated with the whole pelvic chemoradiation in improving the rate of complete pathological response to treatment in patients with FIGO stage IB2-IVA cervical cancer. Patients with stage IIB and III-IVA disease accounted for roughly 76% and 15%, respectively.

It is arguable if that kind of stage proportional distribution could influence the results - a high rate of complete pathological response to chemoradiation and a very encouraging local control rate with an acceptable toxicity profile. The study got criticized by H.B. Govardhan, MD, and colleagues from India not only for stage distribution but also because of the total duration of treatment.

L. Cetina published the first prospective randomized controlled phase III clinical study in 2013 (13). Researchers wanted to demonstrate that RH could result in improved outcomes in FIGO stage IB2-IIB cervical cancer when compared with standard intracavitary brachytherapy after identical chemoradiation. To optimize the efficacy of chemoradiation, a combination of gemcitabine and cisplatin was delivered based on the results of a phase II trial where a high Path CR rate of 77.5% and a survival rate >95% was observed at a median follow-up of 20 (6-29) months (14). The results indicated that the three-year PFS and OS were comparable in both groups, as were the proportions of local and systemic failures. The authors proposed that in patients receiving efficacious chemoradiation, RH rather than normal intracavitary brachytherapy did not reduce survival. However, as the study was not a non-inferiority trial, it was unable to demonstrate that RH following concurrent chemoradiation with cisplatin and gemcitabine could improve survival outcomes.

Gallotta and colleagues went above and beyond to reduce surgical complications and improve clinical results by implementing laparoscopic hysterectomy (LH) following chemoradiation. This was the first prospective, phase II clinical trial that looked at the feasibility and post-operative morbidity of radical LH and pelvic + aortic lymph node dissection (PLND) in LACC patients who had received preoperative CCRT (15). The trial enrolled 58 individuals with FIGO Stage IB2-III. OS or DFS were not included as study outcomes. Following chemoradiation, 44.8 % of pathologically complete responses were reported. The study findings indicated that for individuals with LACC who had undergone preoperative chemoradiation laparoscopic RH was the feasible option with peri-operative outcomes comparable to those observed in patients with early-stage CC and LACC receiving neoadjuvant chemotherapy.

Table 1. Adjuvant Hysterectomy Studies

Study	Study type	N of P.	FIGO stage	Treatment	Comparison	Median Follow up time	Findings		
							OS	DFS	Surgical complications
Ferrandina et al 2007 (9)	Prospective phase II clinical trial	161	IB2-IVA	EBRT in combination with cisplatin and 5-fluorouracil followed by RH	no	28 (3–126 months)	2-year OS 97% and 5-year OS 90%,	2-year DFS 91% and 5-year DFS 83%	Intraoperative – 8.5% Early postoperative G3 – 3.3% G2 – 7.9% Late postoperative – 6.6% ALL G3 – 9.9%
Fanfani et al. 2009 (10)	Retrospective observational descriptive review	39 AH	III B	CCRT followed by AH (median 44.1 Gy; range - 39.6-50.4 Gy) in combination with cisplatin and 5-FU.	no	33 (3 – 80 months)	3-year OS was 70.0%	3-year DFS was 67.6%	G3 – 20% G2 – 48.6 % G1 – 80%
Ferrandina et al 2010 (11)	Prospective phase II clinical trial	174	IB - IVA	CCRT (39,6 – 50,4 Gy combined with cisplatin (20 mg/m2, 2-h intravenous infusion) and 5-FU (1,000 mg/m2, 24-h continuous intravenous infusion) (both on days 1–4 and days 27–30)	no	58 (3–168 months)	3-year OS were 82.5% and 77.4%	3-year DFS were 77.0% and 75.5%	Intraoperative only G1 – 8% Early postoperative G3/4 – 3.4% G1/2 – 16.6% Late postoperative G4 – 1,16% G3 – 3,4 % G1/2 – 8%
Cetina et al 2013 (13)	Prospective randomized controlled phase III clinical trial	211 (AH 111pt and BCT 110pt)	I B2 – II B	CCRT 50,4 Gy concurrently with six courses of cisplatin at 40 mg/m2 and gemcitabine at 125 mg/m2 per week	Brachytherapy	36 (3 – 80 months)	3-years OS was 74.5% vs 76.3%	3-year DFS was 71.7% vs 74.8%	NA
Ferrandina et al 2014 (12)	Prospective phase II clinical trial	103	I B2-IV A	CCRT followed by AH (39,6 Gy to pelvis + 10,8 Gy boost to primary tumor and Parametria) in combination with cisplatin (20 mg/m2, 2-h IV, on days 1-4 and 26-30 of treatment) and capecitabine (1300 mg/m2/daily, orally) during the first 2 and last 2 weeks of treatment.	no	36 (7 – 85 months)	3-years OS was 86.1%	3-year DFS was 73 %	All – 25% G3 – 3% G2 – 8% G1 – 13%
Rem et al 2014 (16)	Retrospective observational descriptive review	43	IB - IIB	CCRT followed by AH (40 to 46 Gy in 20 to 23 fractions and concurrent weekly low-dose cisplatin in a dose of 40mg/m2) plus vaginal cuff brachytherapy after surgery	no	29 months	5-years OS 85.5%	5-years DFS 82.1%	G3 – 6,9 % (3pt) G2 – 60,4% (26pt) G1 – 37,2% (16pt)
Gallotta et al 2015 (15)	Prospective phase II clinical trial	58	IB - III	CCRT followed by AH (total dose of 45-50,4 Gy combined with cisplatin and 5-fluorouracil)	no	22 (5-50 months)	NA	NA	All – 40% G3 – 7.25% G2 – 14.5% G1 – 18.25%
Haas et al 2017 (17)	Retrospective observational descriptive review	248 (87 AH and 161 BCT)	IB1 - IVA	CCRT followed by laparoscopic AH or brachytherapy (EBRT median dose of 50,4 Gy combined with 20 mg/m2 cisplatin and 1000mg 5-FU (/m2 KOF) on days 1–5 in the 1st and 5th week of treatment	Brachytherapy		5-years OS (with and without residual after CCRT) 41-80% vs 76,9 -82%	5-years DFS 73,9 – 75% vs 84.6-100%	NA
Yoshida et al 2019 (18)	Retrospective observational descriptive review	136 (AH 50pt and 76pt BCT)	IB2-IIB	CCRT followed by AH ot intracavitary brachytherapy (EBRT 50.4Gy in combination with two course of chemotherapy - cisplatin (70 mg/m2 on day 1) and 5-fluorouracil (700 mg/m2, 24 h continuous intravenous infusion on days 1–4)	Brachytherapy	64.8 (range 4.8 – 143.9 months)	5-year OS 87.7% vs 66.2%	5-year DFS 78.3% vs 56.9%	G3 – 23,1% G ½ - 32.9% No adverse events in 44%

Notably, none of the previous studies proved that RH could enhance outcomes with decreased toxicity. Therefore, the use of RH has been questioned, and the simple hysterectomy (Piver I) after chemoradiation has been considered an alternative by Haas and colleagues (17).

They retrospectively analyzed the cancer registry of Saxony-Anhalt, a federal state of Germany. Reports of 248 patients were eligible for analysis from which 161 received brachytherapy, and 87 underwent a simple hysterectomy. The researchers discovered that the reaction to chemoradiation has an effect on the result. For patients with clinically no residual tumor the estimated 5-year DFS rate was 100% in the control group and 73.9 % in the surgical group ($p = 0.103$), while it was 75.0 and 84.6 % in the group of patients with residual lesions, respectively ($p = 0.028$). The 5-year DOS rate for patients with residual tumor was 41.7 and 76.9 %, respectively, in groups 1 and 2. This difference was statistically significant (Fig. 3b; $p = 0.011$).

Furthermore, the estimated DOS for patients without residual tumor was also similar in group 1 and group 2 and was estimated to be 80.0 and 82.0%, whilst in individuals with the residual tumor, it was 41.7 and 76.9% in group 1 and 2, respectively. Importantly, this difference was statistically significant ($p = 0.011$). The authors concluded that sample hysterectomy following chemoradiation without brachytherapy is feasible in selected patients and that the survival benefit of hysterectomy in patients with residual illness following RCT should be validated in prospective randomized trials.

Yoshida and colleagues (18) recently published a study comparing the outcomes of neoadjuvant concurrent chemotherapy and radiation followed by RH and PLND in contrast with definitive chemoradiation using inverse probability of treatment weighting (IPTW). While the Kaplan–Meier curves for PFS and OS did not differ significantly across groups ($p = 0.219$ and 0.217 , respectively), the Kaplan–Meier curves for IPTW adjusted PFS and OS were considerably longer in the NACRT group than in the CRT group ($p = 0.027$ and $p = 0.017$, respectively). In the NACRT and CRT groups, IPTW adjusted 5-year DFS rates were 78.3% and 56.9%, and IPTW adjusted 5-year OS rates were 87.7% and 66.2%, respectively. Surprisingly study suggested that surgery after CRT reduced pelvic recurrence and, as a result, provided favourable PFS and OS.

3DCRT and IMRT Boost - technique matters

First papers about treating cervical cancer with EBRT alone appeared in the early 1960s. All the papers were fragmented, had shorter follow up periods and all the results were not summarized as conclusions. Castro et al. conducted a retrospective analysis of 108 patients treated with EBRT alone in 1970, concluding that 50 Gy was insufficient for cervical cancer control and that a 20 Gy boost was required (19). In 1983 Ulmer reported they had similar results with EBRT alone in comparison to combined intracavitary and EBRT (5-years OS by stages: II – 75 %, III – 30%, IV – 13%) (20). They obtained homogeneous dose distribution with plan parameter alterations. Radiation-induced side effects were observed in most of the patients and also similar to somewhat reported before with combined treatment. There was no toxicity in the G4 to 5 ranges. Notably, all 150 patients had poor prognoses - they were older, had locally advanced disease, and had poor performance status. Soon after, In 1986 Montana studied survival rates and the relationship between complications and point A doses for stage III CC (21). Eighty-eight patients were treated with EBRT alone in that trial, out of 203. Results showed that 2 years DFS was more desirable for the combination therapy group, but this difference was not maintained exceeding 5 years.

The article, published by Lisa Helen Barraclough in the International Journal of Radiation Oncology Biology and Physics in 2008, reported the results of the retrospective observational descriptive review (22). The study included 44 patients treated with EBRT boost. A total dose of 60–65 Gy was given to 31 patients (71%). Two patients received 67.5–70 Gy, 11 patients received 54–58 Gy. During a median follow-up of 28 months (range, 3–96 months), 2-year OS was reported to be 64 % and 5-year OS to be 49.3 %, while treatment-related toxicity was relatively tolerable – G3 – 2%, G2 – 16 %, and G1 – 22.5 %. According to our present knowledge, the results could be disputed because the research population has only received concurrent treatment since 2001. A dose of 40 mg/m² with a maximum of 70 mg is given weekly during radiotherapy as long as the treatment is tolerated. From 44 patients, chemotherapy was administered to 19 patients (43%) - neoadjuvantly to 11 patients and concurrently to 8. However, this study demonstrates that an EBRT boost could be a reasonable option when brachytherapy boost cannot be performed.

Table 2. 3DCRT and IMRT Boost

Study	Study type	N of P.	FIGO stage	Chemo	RT technique	Dose	Comparison	Median Follow up time	Findings		
									OS	DFS	Toxicity
Barraclough et al 2008 (22)	Retrospective observational descriptive review	44	IB-IVA	Cisplatin	3DCRT	phase 1 volume was 40–45 Gy in 20 fractions over 26 days. A dose of 15–25 Gy is given in 8–10 fractions given over 10–12 days for phase 2	no	28 (3–96 months)	2-year OS 64% and 5-year OS 49.3%,	NA	G3 – 2% G2 – 16% G1 – 22.5%
Park et al 2010 (23)	Prospective clinical trial	9	IIA-IIIB	Cisplatin	3DCRT	whole pelvis RT with a median dose of 50 Gy (range, 40-50 Gy) before the boost. The median dose of the boost was 30 Gy (range, 25-30 Gy).	no	17.6 (4.9-27.3 months)	NA	2-year DFS 52%	G3 – NO G2 – 22% G1 – 55.5%
Matsuura et al 2012 (24)	Prospective clinical trial	16	IIB-IVA	NA	3DCRT	The median total dose was 66 Gy (range: 66–73 Gy) on the CCB The median total dose was 60 Gy (range: 60–66.2 Gy) on the CF schedule.	No (different fractionations were compared CF vs CCB)	40 months (range: 6–93 months)	3-years OS 43.8%	NA	G3 – NO G2 – 25% G1 – 43%
Kadkhodayan et al 2013 (25)	Prospective clinical trial	30	IIB-IIIB	Cisplatin 35 mg/m2 weekly	3DCRT	50 Gy within 5 weeks to whole pelvic that has followed by a localized boost dose on tumor to 70 Gy	No	25.5 months (rang: 11-56 months)	3-years OS 39.1% (±9%)	NA	G4- Diarrhea 6.6% G3- Neutropenia 13.3%, Diarrhea 6.66% G2- Anemia 23%, neutropenia 33.3%, Nausea and vomiting 10%, Diarrhea 3% G1 – Anemia 33%, Neutropenia 30%, Nausea and vomiting 3.33%, Diarrhea 6.66%
Mazzola et al 2016 (26)	Prospective clinical trial	30	II-III	Cisplatin 40 mg/mq	SIB - VMAT	EBRT - 66 Gy to the macroscopic disease and 54 Gy to the pelvic nodes in 30 fractions	no	32 (8-48 months).	3-years OS 93%	NA	G3 – NO G2 – 3% G1 – 63%
Kim et al 2017 (27)	Multicenter Retrospective Study	75	I-IV	NA	3D-CRT 24pt (32%) IMRT 51pt (68%)	46 Gy (range, 40-54 Gy) for whole pelvis and 24 Gy (range, 9-35 Gy) for Boost	no	33 months (range, 2-104 months)	5-years OS 75%	5-years DFS 54.7%	G3 – 12% G1/2 - NA
Delgado et al 2019 (28)	Retrospective observational descriptive review	92 (55 EBRT and 37 ICB)	IB1-IVA	Cisplatin	3DCRT	pelvic 3D conformal EBRT (range, 45-50.4 Gy) and 3D conformal EBRT boost (16.2 Gy)	ICB	67 months (range: 5-144 months)	5-years OS 58% (EBRT) vs. 82% (ICB);	5-years DFS 38% (EBRT) vs. 79% (ICB);	NA
Lazzari et al 2020 (29)	Retrospective observational descriptive review	25	IIB-IVB	18 (72%) patients received weekly cisplatin, seven (28%) cisplatin and paclitaxel	IMRT	EBRT of 45–50.4 Gy in 25–28 fractions (1.8 Gy/fraction) to pelvis ±para-aortic lymph nodes and sequential IMRT boost	no	26months (range:4 – 77 months)	2-year OS 67%	2-year DFS 55%	G3/4 – NO Acute G2 – 12 % G1 – 28% Late G2 – 12% G1 – 21%

Few prospective clinical trials (23-25) tried to determine the clinical outcomes and feasibility of EBRT for locally advanced cervical cancer when patients were unable to receive an intracavitary brachytherapy boost. Although the results of 3DCRT-EBRT were poor and had never been comparable to the results of brachytherapy, EBRT was still considered a promising and feasible modality as an alternative radical therapy in cases where ICBT could not be administered. Mazzola and colleagues reported the first prospective clinical trial when the VMAT technique was used instead of 3DCRT techniques in 2016 (26). By the time, there have been no reports of intensity-modulated radiotherapy used to boost the central pelvis in place of brachytherapy and notably, there was a need of new clinical trials evaluating potential role of IMRT boost in cervical cancer treatment. After the first introduction in clinical practice, IMRT was considered to have considerable potential in treating women with gynecologic malignancies. Initial clinical experience showed that IMRT resulted in less acute and chronic gastrointestinal toxicity and spared the pelvic bone marrow, reducing the risk of hematologic toxicity. Soon after, IMRT was considered to be a dose-escalation method instead of brachytherapy. Numerous authors reported promising data about IMRT plane evaluation, dosimetry, and toxicity. Not surprisingly, the results reported by Mazzola et al. were completely different from the previously published data. During a median follow-up of 32 months, the 3-years OS was 93%. The absence of pelvic nodal recurrences suggested that a higher dose to the PET-positive nodes employing the SIB approach could be an effective strategy. Although the data were preliminary, these results seemed unexpected compared to what was suggested in the literature: In the treatment of cervical cancer, the LC rates are related to the biologically equivalent dose: high doses (80-95 Gy to the primary tumor) administered over a short time (inferior to 50-55 days) has significant impact on LC and OS. There is a need for long term results and update of this study, which may provide us with a much more interesting data.

Delgado et al. (2019) published the first retrospective study comparing the results of EBRT boost versus brachytherapy boost (28). But the RT technique applied in the study was 3DCRT vs. intracavitary BT. The 5-year OS rate in the BT-IC group (82 %) was greater than in the EBRT group, as expected (68 %). However, when compared to other published studies, the outcomes of 3DCRT were still superior. The dominance of the lower FIGO stage (IIB) and the retrospective aspect of the study could be the main grounds for criticism, which could lead to better outcomes for 3DCRT than previous published series. Lazzari published a study in the International Journal of Gynecological Cancer in 2020 regarding the clinical outcomes of IMRT in locally

advanced cervical cancer in the absence of BT (29). Three main facts were highlighted: Six months after the IMRT boost, 22 (88 %) of the 25 patients had complete local control of the cervix; For all stages, the 2-year OS, DFS, and local control (LC) rates were 67 %, 55 %, and 78 %, respectively; Following the delivery of an IMRT boost, no G3-4 toxicities were noted (Table 2).

SBRT boost

Briefly, reviewing historical aspects of SRS/SBRT, during the late 1980s and early 1990s, SRS grew rapidly. The main indications for this kind of treatment were pain syndromes or movement disorders. Sturm et al. were one of the first authors reporting brain metastasis as an indication for SRS in 1987. SBRT developed about a decade later than SRS but was based on similar principles. In Karolinska Hospital Stockholm, SRS procedures were well utilized. Ingmar Lax and radiation oncologist Henric Blomgren reasoned that similar local control outcomes could be achieved at different body sites with one or a few focally delivered fractions, even if targeting and immobilization issues for sites outside of brain were more much difficult. Lax and Blomgren described their technique in 1994 (30) and in 1995 reported clinical outcomes in 31 patients with 42 malignant tumors located in the liver, lung, or retroperitoneum. They achieved local control in 80 % of cases. David Larson visited the Karolinska Hospital in 1993 as an observer. He brought Lax and Blomgren's technique back to his home institution, where he treated 150 patients during 1993–1995. New treatment delivery techniques (i.e., dynamic-arc treatment and intensity-modulated radiotherapy [IMRT]) and availability of highly accurate immobilization and repositioning systems made SBRT possible to relatively small pelvic tumors. Optimal repositioning with fiducial markers and an inflatable rectal probe had been reported for prostate cancer patients in the early 2000s.

All mentioned above made a basement for future research of using SBRT for cervical cancer and became an inspiration for several studies and clinical trials investigating the efficacy and toxicity of SBRT for cervical cancer and its impact on survival. Although there are no randomized controlled trials evaluating its effectiveness of toxicity, SBRT has been adopted as one of the treatment options for recurrent, oligometastatic, and sometimes in up-front settings for gynecologic tumors, alone or with EBRT. Several retrospective clinical reports and retrospective dosimetric reports have shown that SBRT appears to be a reasonable treatment option for patients unable to receive intracavitary treatment.

Haas et al. (31) and Marnitz et al. (33) used the Cyberknife to track the previously implanted gold fiducials in the cervix for precise SBRT boost delivery resulting in a high rate of local control (both 100%).

Haas and colleagues reported no G3 or higher toxicity, while Marnitz and colleagues reported a high rate of treatment-related toxicity. Because of the shorter median follow-up time (only 14 months for Haas et al. and six months for Marnitz et al.), there is no information reported about late toxicity, 3- or 5-years OS or DFS. Hsieh et al. reported the 3-year OS 46.9% and the 3-years DFS 77.8% but also accounted for a longer overall treatment time (median = 79 days) and included patients with advanced disease. One patient presented with grade 3 diarrhea, and another had grade 3 thrombocytopenia during treatment.

The study had several limitations: no statistical conclusions can be drawn due to a small number of cases, the retrospective study design, a short follow-up period, so long-term results and close monitoring are further required, not all the patients had implanted fiducial markers, so the radiotherapy margin could not be reduced effectively, even with image-guided technique, which could be the main reason for late G2 rectal toxicity (33,3%, 3/9pt) in the study.

Table 3. SBRT Boost

Study	Study type	N of P.	FIGO stage	Machine	Treatment	Comparison	Median Follow up time	Findings		
								OS	DFS	Toxicity
Haas et al 2012 (31)	Retrospective chart review	6	NA	Cyber knife	whole pelvis RT 45–50.4 Gy in 1.8 Gy/fraction followed by SBRT boost (20Gy/5fx or 19.5/3fx)	no	14 months	NA	1-year DFS 100%	G3/4 – NO G2 – NA G1 – 66% (4/6 pt)
Hsieh et al 2013 (32)	Retrospective observational descriptive review	9	IIB to IVA	Tomotherapy	WPRT followed by SBRT (27-16 Gy/5–9 fractions)	no	13 months (range: 4–40 months)	3-year OS 46.9%	3-years DFS 77.8%	G3 -Diarrhea 11% cytopenia – 11% G2 -Diarrhea – 11%, GU – 11%, cytopenia – 22% G1 – Nausea 100%, Diarrhea - 78%, GU – 89%, cytopenia – 89%
Marnitz et al 2013 (33)	Retrospective observational descriptive review	11	IIB-IIIIB	Cyber Knife	WPRT of 50.4Gy with SIB to parametrium 59.36Gy followed by SBRT (30Gy/5 fractions)	no	6 months	NA	NA	G4 – cytopenia – 9% G3 – cytopenia 27%, G2 – Cytopenia - 63%, GU – 18%, GI-18% G1 – cytopenia - 36%, GU – 81%, GI – 81%, vaginal-100%
Mantz et al 2015 (34)	Prospective clinical trial	40	NA	NA	WPRT 45Gy followed by SBRT (40Gy/ 5fx delivered over a 10-day)	no	51 months	NA	2-years DFS 77.5%	NA
O'donnell et al 2018 (35)	Retrospective database review	15,905 14,394 (90.5%) brachytherapy 42 (0.8%) SBRT 1468 (9.2%) IMRT	I-IVB	NA	WPRT followed by boost – ICB vs IMRT vs SBRT	ICB vs IMRT	NA	Median OS ICB 99.1 Months, SBRT - 30.6 months, IMRT - 29.8 months. With Propensity-Matched Analysis there was no significant difference in overall survival between those who received SBRT boost and those who received a brachytherapy boost (HR = 1.477, 95% CI = 0.746Y2.926, P = 0.263).		
Albuquerque et al 2020 (36)	A Phase II Trial	15	IB2-IVB	NA	whole-pelvis radiotherapy (45 Gy in 25 fractions with SIB to positive nodes) followed by SBRT (28 Gy/4 fractions)	no	19 months	2 years OS 53.3%	2 years DFS 46.7%	G3/4 - 26.7% Study was closed early due to toxicity concerns.

In 2019, O'Donnell et al. (35) published the results of a database evaluation of 15,905 women with CC, of whom 14,394 (90.5%) underwent brachytherapy, 42 (0.8%) received SBRT, and 1468 (9.2%) received IMRT. Patients who received brachytherapy as a boost survived on average 99.1 months, those who received SBRT as a boost survived on average 30.6 months, and those who received IMRT as a boost survived on average 29.8 months. There was no significant difference in overall survival between those who received SBRT boost and those who received brachytherapy boost using Propensity-Matched Analysis. Multivariable analysis identified the following factors as being significantly associated with decreased overall survival: increasing age, insurance, histology of adenocarcinoma, progression of the disease's FIGO stage, pelvic nodal involvement, presence of distant metastasis, and receiving IMRT rather than brachytherapy.

The latest clinical trial reported by Albuquerque et al. (36) in 2020, was discontinued early due to toxicity concerns (G3/4 toxicity- 26.7%). Fifteen patients were treated with whole-pelvis radiation (45 Gy in 25 fractions with SIB to positive nodes), followed by SBRT boost (28 Gy/4 fractions) in 15 patients. The local control rate was 70%, which is equivalent to the lower range for standard therapy in patients with similarly advanced stage and bulky disease, where the local control rate ranges from 75-85 %, but lower than reported in previous SBRT studies. A significant number of participants developed regional and systemic recurrences related to the high number of bulky advanced-stage tumors. These systemic failures with significant co-morbidities were a significant driver of patient mortality in this trial (Table 3).

DISCUSSION

Since chemoradiation was established, the prognosis of patients with LACC has improved. However, some patients still develop treatment-resistant tumors and have a poor prognosis. During this review, a huge gap in the literature was noted about alternatives to brachytherapy. There are no prospective randomized controlled trials with enough sample size evaluating efficacy or toxicity for different approaches compared to brachytherapy. Most studies have a very small sample size, short follow-up times and most were retrospectives in nature. Radiation therapy dosing regimens and fractionations varied widely from one study to the other, as well as techniques of hysterectomy. Studies also used different parameters of survival and toxicity, making it difficult to perform across-studies comparisons and dose-toxicity evaluation. Theoretically, SBRT is the most certain technique among all EBRT modalities in terms of its ability to simulate a BT dose distribution with a steep dose gradient and, as a result, achieve the same treatment outcomes as ICB, at least theoretically. SBRT allows for the delivery of high-dose chemotherapy directly to the tumor while conserving as much healthy tissue as is reasonably practicable. SBRT has been shown to be superior in a few dosimetric experiments due to its great target coverage and OAR sparing properties. But whether an extremely high dose within the tumor is required radiobiologically remains a matter of debate and will not be discussed in detail in this paper. Although the BT profile (characterized by an exceptionally high dose within the applicators) is exceedingly effective, it cannot match with the homogeneity of the EBRT dose throughout the target volume.

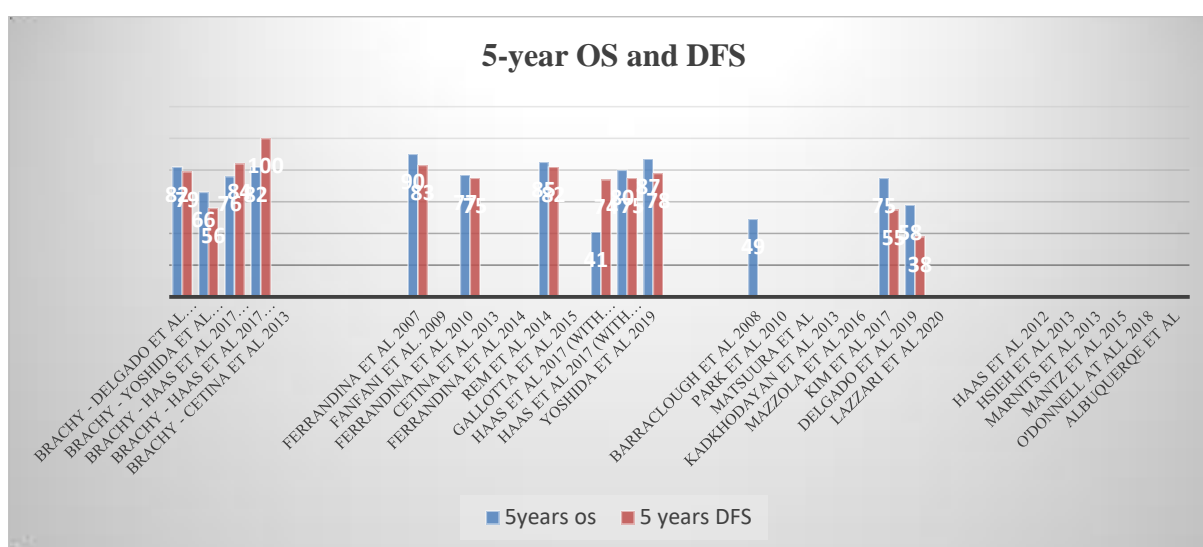


Figure 2. 5-years OS and DFS

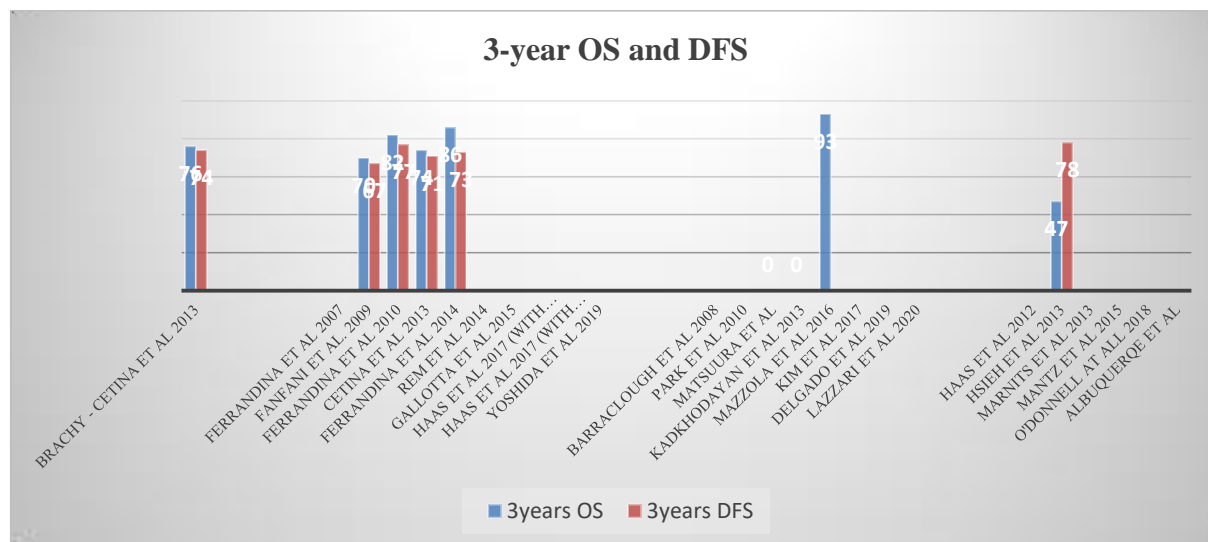


Figure 3. 3-years OS and DFS

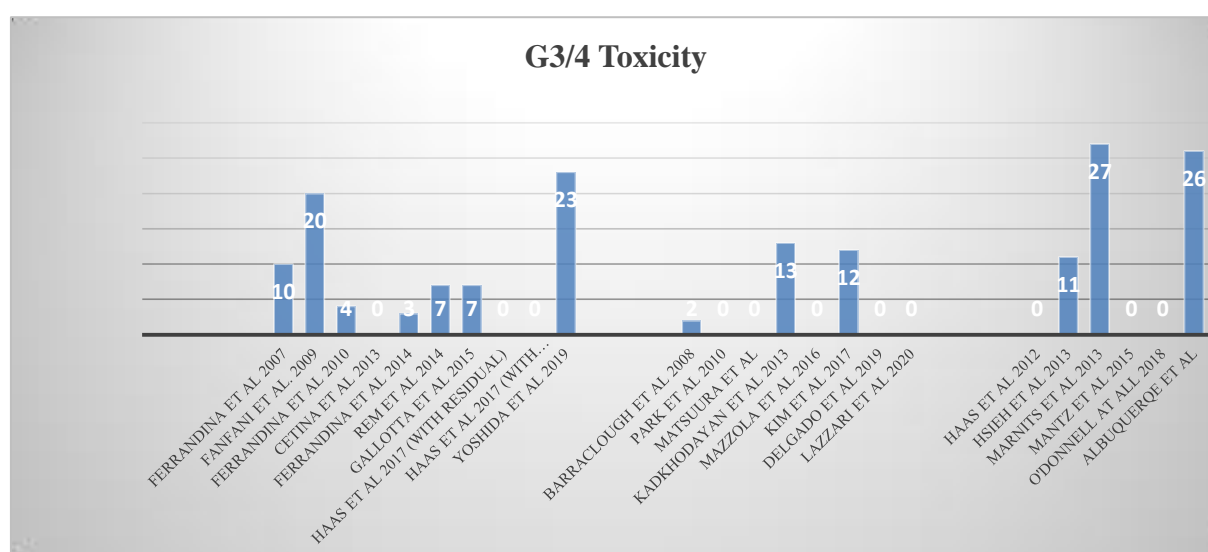


Figure 4. G3/4 Toxicity.

If we look to our results from the standpoint of 5-years OS and DFS (Fig. 2), notably, there is a look of date for EBRT techniques; we have no data about SBRT. Unlikely to EBRT/SBRT, we have more data for AH. Median 5-years OS and DFS after AH was 76.6% (range: 41%-90%) and 77.8% (range: 74%-83%). Median 5-years OS and DFS after EBRT (3DCRT - 187pt/IMRT 24pt) 59.9% (range: 49%-75%) and 46.5% (range: 38%-55%). We have no 5-years data for the SBRT boost.

In terms of 3-years OS adjuvant hysterectomy provides the same results as brachytherapy 78% (range 70%-86%) vs. 76%, while EBRT 3-years OS is 58.6% (range: 39.1%-93%) and 46% for SBRT (Fig.3). There is only one study reporting 30years DFS after SBRT (Hsieh et al. 2013) – 78%, which seems quite promising. As for toxicity, SBRT is associated with more treatment-related toxicity (Fig.4.); however, reported as acceptably by most authors.

Rate of G3 toxicity for hysterectomy, EBRT and SBRT were 10.5% (range: 3%-23%), 3.8% (range:0-13%) and 16% (range: 0-27%) respectively.

CONCLUSION

When all these alternative approaches to ICB are evaluated, adjuvant hysterectomy appears to have treatment outcomes comparable to standard of care, while SBRT appears to have only modest yearly results at the moment. As a result, the majority of writers believe that neoadjuvant chemoradiation followed by radical surgery or SBRT may be a realistic therapeutic option for patients with LACC, not merely when ICB is unavailable, technically impractical, or rejected. Large prospective randomized controlled trials are required to conclusively demonstrate or invalidate non-ICB alternatives for cervical cancer treatment.

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