Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol. 5 No. 3 (2024): March 2024 Issue
https://doi.org/10.51168/sjhrafrica.v5i3.1103
Original Article

AN INVESTIGATION INTO KRUKENBERG'S TUMOUR AT A TERTIARY REFERRAL CENTRE: A COHORT STUDY.

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Abstract

Objectives

This study aims to distinguish women having Krukenberg cancer and confirm the significance of non-curative surgery

Methods

In this retrospective study, 107 patients with Krukenberg cancer as well as ovarian tumors were chosen from hospital records. The radiological studies were carried out by means of pre-operative abdominal/pelvic CT scans. The radiology results after evaluation by a diagnostic radiologist provided details on the size of the tumor, its metastases, the involvement of lymph nodes, and ascites extracted. Additionally, CT images were processed and standardized for analysis, including tumor segmentation and image resizing.

Results

The study included 107 patients diagnosed with Krukenberg tumors (n=58) or ovarian tumors (n=49), with 72.5% diagnosed at stage IV, highlighting advanced disease. Surgical resection was performed in 73.3% of patients, emphasizing its importance in management. Metachronous tumors occurred in 54.2% of patients, indicating metastasis of the ovarian tumor post-primary tumor diagnosis. Treatment responses varied, with 38.5% responding to systemic therapy, while 70.7 % experienced disease progression. Additionally, age and elevated CA125 levels (OR: 2.49; 95% CI: 1.50–5.43; $p < 0.001$; OR: 1.61; 95% CI: 1.37–2.60; $p = 0.005$) showed significant associations with Krukenberg tumors in multivariable analysis.

Conclusion

The study underscores the significance of surgical resection and highlights the diagnostic value of CA125 levels in managing Krukenberg tumors.

Recommendation

The study recommends further investigation into the utility of CA125 levels as a diagnostic marker and emphasizes the importance of timely surgical intervention in the management of Krukenberg tumors.

Keywords: *Krukenberg Tumors, Ovarian Metastases, Surgical Resection, Cancer Antigen 125 Levels, Prognostic Factors*
Submitted: 2024-01-12 Accepted: 2024-02-20

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Introduction

Secondary outgrowths in the ovaries usually arising from the gastrointestinal cancers such as colorectal or stomach tumors are known as Krukenberg tumors [1]. About 80 % of these tumors are seen as bilateral tumors, and these primarily affect women [2]. In particular, it has been noted that young people manifest serious health conditions due to these tumors. Earlier research on Krukenberg tumors has frequently shown limited response to conventional treatment and mainly linked to a worse prognosis when compared to metastatic cancers originating from the same primary sites [3]. They present a therapeutic challenge because of their unique aversion to going into shock and their tendency to grow into enormous masses even after being treated elsewhere in the body [4, 5].

Identifying the primary cancer site and starting palliative chemotherapy to control systemic disease is usually the first-line strategy to treat metastatic gastrointestinal cancers, including those with Krukenberg tumors. This contrasts the therapeutic regimen adopted for certain primary ovarian cancers, in which neoadjuvant chemotherapy is chosen after surgical intervention and shows proven survival benefits [6]. Yet, due to the limited effectiveness of the systemic therapy, the surgical removal of metastases or metastasectomyis widely utilized, particularly if debulking and resection of the tumor from the primary main tumor is possible [7, 8]. In line with this context, studies have demonstrated that a combination of chemotherapy and metastasectomy greatly increased the vitality rates in women with Krukenberg tumors [7, 9].

The primary step in treating Krukenberg tumors is to distinguish it from primary ovarian cancers as this guides in selecting the appropriate management decisions. However, the clinical symptoms, biomarkers, and latest diagnostic imaging techniques often fail in reliably differentiating Krukenberg tumors from the latter [10, 11].

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The present study aims to distinguish women having Krukenberg cancer and confirm the significance of non-curative surgery.

Materials and Methods

Study design

A retrospective cohort study

Study setting

The study was conducted in MGM Medical College, Jharkhand, India for a period of 1 year and aimed to assess patients diagnosed with Krukenberg cancer or malignant epithelial ovarian tumors.

Inclusion and exclusion criteria

The study cohort encompassed women aged 18 and above with histologic confirmation of Krukenberg cancer. The patients who did not have histological confirmation of Krukenberg tumors were excluded from this study. In the case of women with ovarian tumors, participants with grade 3/4 histological confirmation and/or stage 3/4 disease were included in the study. Moreover, patients aged below 18 years and with no accessible pre-operative pelvic/ abdominal CT scans as well as diagnostic imaging results taken prior to excisional oncologic surgery were not part of the study.

Study size

The study retrospectively identified 107 patients diagnosed with Krukenberg cancer over the past 1 year.

Study setting

The study made use of the patient records stored in the hospital to take place in a retrospective manner. In addition to this, the cancer centre registries were also comprehensively examined to ensure that all the patients were involved in the study. The procedures of data collecting and analysis were carried out inside the hospital's framework.

Patient Selection

Patients were retrospectively identified from hospital's patient records spanning for 1 year using specific keywords like Krukenberg tumors and metastatic ovarian cancer. The baseline characteristics, molecular traits, tumor pathology, therapeutic history, and tumor marker levels, of all the patients were reviewed.

Radiographic Evaluations

Pre-operative CT scans of the abdomen and pelvis with associated radiological interpretations of all the patients were obtained for analysis. Features such as the size of the ovarian masses, the existence of metastatic peritoneal cancer, metastasis to distant site, involvement of lymph nodes, ascites, and the nature of the masses (cystic or solid) were extracted from radiology reports. A diagnostic radiologist assessed the CT scan quality and radiologic features of the Krukenberg tumors autonomously.

Image Processing

The diagnostic radiology database of the hospital provided the CT scans with intravenous contrast. An image reviewer was used to process these photos and convert them to Portable Network Graphics format. Tumor segmentation involved the process of delineating the tumor by selecting a rectangular region of interest and ensuring uniformity in image size, which was then standardized to the desired pixels.

Bias

The retrospective nature of the study as well as its reliance on the patient records might give rise to selection bias and eliminate patients with insufficient documentation. Furthermore, the inclusion of only certain keywords for identifying patients can miss situations when clinical records do not specifically identify metastatic ovarian cancer or Krukenberg tumors.

Ethical consideration

The study obtained institutional ethics approval, and individual consent from each patient for retrospective analysis was appropriately obtained to ensure compliance with ethical guidelines.

Statistical Analysis

Student's t-test was used for statistical comparison of the continuous and categorical variables. The survival analysis employed Kaplan-Meier method for assessing time-to-event data, while logistic regression assessed the predictors of Krukenberg cancer and ovarian tumors.

Results/Outcomes

Participants

This study comprised of 107 patients diagnosed with Krukenberg tumors or ovarian tumors. Notably, 72.5% of patients were diagnosed at stage IV ovarian tumors, indicating advanced disease condition. Additionally, 73.3% of patients underwent primary tumor resection, hinting the importance of non-curative surgery in the treatment of Krukenberg cancer. Among the histological features, grade 3 tumors were the most common, comprising 39.4% of cases, indicating aggressive tumor behavior. Furthermore, molecular analysis revealed KRAS mutations in 50.0% of cases, suggesting potential therapeutic implications. Moreover, 54.2% of patients had metachronous Krukenberg tumors, indicating the occurrence of metastatic ovarian cancer after the initial diagnosis of the primary tumor. (Table 1).

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Table 1: General data collected from the hospital records

Characteristics	Types	Total (n = 107)	Missing (%)
Types of cancer (%)	Gastrointestinal	52 (48.5)	0
	Stomach or esophagogastric junction	22 (21.1)	
	Endocrine	10 (8.8)	
	Mammary	8 (7.4)	
	Appendicular	5 (4.7)	
	Small intestine	3 (2.8)	
	Pancreatic gland	5 (4.7)	
	Choledochal	2 (2.6)	
Stage at diagnosis (%)	I	6 (5.8)	0
	II	6 (5.8)	
	III	20 (19.3)	
	IV	75 (72.5)	
Primary excisional therapy (%)	No	30 (28.2)	0
	Yes	77 (73.3)	
Grade (%)	1	19 (18.4)	0
	2	25 (26.4)	
	3	38 (39.4)	
	4	25 (26.4)	
Mucilaginous (%)	Absence	79 (83.5)	12.1
	Presence	15 (16.5)	
Signet (%)	Absence	67 (70.2)	11.2
	Presence	28 (29.8)	
Mismatch repair impairment (%)	Absence	31 (95.4)	69.1
	Presence	2 (4.6)	
Kirsten rat sarcoma viral oncogene homolog (KRAS) (%)	Absence	18 (50.0)	66.3
	Presence	18 (50.0)	
BRAF proto-oncogene serine/threonine kinase (%)	Absence	20 (92.9)	79.4
	Presence	2 (7.1)	
HER2/neu (%)	Absence	19 (86.0)	80.3
	Presence	3 (14.0)	
Classes of Krukenberg cancer (%)	Metachronous	58 (54.2)	0
	Synchronous	49 (45.8)	

Among the patients, 77.4% underwent primary tumor debulking while 22.6% did not undergo resection. The median levels of tumor markers were found to be elevated, with an average CA125 level of 41.0 U/mL, average CA19-9 level of 63.4 U/mL, and median CEA level of 4.6 ng/mL (IQR: 2.4-26.0). Regarding treatment sequences, 46.7% of patients underwent surgery alone, while 31.0%

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received surgery followed by systemic therapy. Notably, 38.5% of patients exhibited a response to systemic therapy, while 70.7 % experienced disease progression after Krukenberg tumor management. Additionally, 55.6% of patients had passed away by the time of data collection, underscoring the significant morbidity associated with Krukenberg tumors (Table 2).

The univariate and multivariable logistic regression analysis results for factors associated with Krukenberg tumors were also examined. Significant associations were found for increasing age and elevated CA125 levels in multivariable analysis. Other factors like CEA levels, distant site metastasis of tumor, ascites, and bilateral ovarian masses, showed varying associations in univariate analysis but were not significant in multivariable analysis (Table 3).

Table 2: Clinical features and therapeutic results in the study cohort

Traits	**Stages**	**Total (n = 107)**	**Missing (%)**
Resection of tumor (%)	Absence	24 (22.6)	0.9
	Presence	82 (77.4)	
CA125 (U/mL), median (IQR)		41.0 (16.0, 183.0)	
CA19-9 (U/mL), median (IQR)		63.4 (14.7, 403.0)	
CEA (U/mL), median (IQR)		4.6 (2.4, 26.0)	
Therapeutic intervention in Krukenberg cancer (%)	Pharmacotherapy	18 (19.6)	17.7
	Pharmacotherapy+ surgical approach	3 (2.7)	
	Surgical intervention	43 (46.7)	
	Surgical intervention+ Pharmacotherapy	29 (31.0)	
Response to pharmacotherapy (%)	Absence	12 (61.5)	81.3
	Presence	8 (38.5)	
Metastases after therapeutic intervention (%)	Absence	27 (29.3)	14.9
	Presence	64 (70.7)	
Fatality (%)	Absence	47 (44.4)	0
	Presence	60 (55.6)	

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Table 3: Analysis of Individual and Multiple Variables Related to Krukenberg Tumors

Characteristics	Krukenberg tumor (n=107)	Levels	OR (95% Cl, P value)	
			Univariate	Multivariable
Age (year)	53.8	Each decade increment	2.17 (1.39–2.71, < 0.001)	2.49 (1.50–5.43, < 0.001)
CA125 (U/mL)	41.0	Each 100-unit per milliliter rise	1.48 (1.30–1.76, < 0.001)	1.61 (1.37–2.60, 0.005)
CA (19-9 (U/mL)	56.7	Each 10-unit per milliliter rise	0.94 (0.89–0.96, 0.14)	–
CEA (ng/mL)	4.3	Each 10-nanogram per milliliter rise	0.13 (0.01–0.38, < 0.001)	0.02 (0.00–0.26, 0.035)
Bilateral ovarian masses (%)	48(52.8)	No	–	–
	43 (47.2)	Yes	0.52 (0.30–0.75, 0.004)	0.26 (0.06–1.12, 0.067)
Distant metastases excluding peritoneal involvement (%)	42 (53.2)	No	–	–
	36 (46.8)	Yes	0.41 (0.21–0.81, < 0.001)	0.52 (0.15–2.16, 0.31)
Peritoneal metastasis (%)	40 (51.0)	No	–	–
	39 (49.0)	Yes	6.72 (3.91–9.87, < 0.001)	3.18 (0.62–17.54, 0.14)
Lymph node metastasis	49 (64.7)	No	–	–
(%)	27 (35.3)	Yes	1.24 (0.71–1.57, 0.29)	–
Ascites (%)	42 (55.6)	No	–	–
	34 (44.4)	Yes	2.37 (1.60–3.53, <0.001)	0.33 (0.07–1.47, 0.16)
Cystic or solid (%)	23 (29.8)	Both	–	–
	27 (35.8)	Cystic	0.72 (0.35–1.75, 0.40)	–
	26 (34.4)	Solid	1.18 (0.48–1.37, 0.72)	–

Discussion

In this study, a systematic evaluation of common clinical, biochemical, as well as radiographic attributes was carried out to identify Krukenberg cancer from ovarian tumors before surgery. The current study's patient cohort reflected the typical prevalence pattern of primary tumors, indicating rectal tumors as the predominant type, aligning with existing literature [12]. However, in contrast to the findings from Asian countries wherein the most prevalent primary source of Krukenberg tumors was identified as gastric cancer, this study showed a different pattern [13]. Similar overall survival (OS) rates and prognostic factors as reported by previous studies were also observed [14-16].

Notably, the current study demonstrated that non-curative surgery, with or without pharmacotherapy, significantly increased the progression-free survival (PFS) and overall survival (OS) in participants with colorectal cancer, consistent with earlier findings [7,8,17,18]. Interestingly, it was noted that with adjustment of the prognostic factors, no statistically significant correlation with OS was observed. This was probably due to the palliative nature of surgery in this study which contrasts with the cytoreductive resection reported in the previous studies [8, 19]. Conversely, Krukenberg tumors originating from gastrointestinal tumors failed to respond well to palliative surgical resection as reflected in terms of lack of prolonged survival, making this distinct from the other studies published in this area [19-21].

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On comparing the average progression-free survival of patients with rectal and gastrointestinal tumors, the former group of patients subjected to tumor resection experienced greater PFS unlike the latter group. This discrepancy might be due to the poor prognosis of advanced gastric tumors when compared to colorectal tumors, besides the reduced performance status scores and severe anemia usually encountered along with Krukenberg tumors arising from gastriointestinal tumors.

While there has been extensive research on the diagnosis of Krukenberg tumors, research focusing on their radiologic and clinical diagnosis compared to primary ovarian cancers are limited [10, 22]. Earlier studies majorly relied on contrasting the CT or MRI imaging outcomes to identify Krukenberg cancer from ovarian tumors [22-24]. These studies depicted characteristic traits like bilateral solid ovarian masses with cystic cavities within the tumor and enlargement of the tumor wall. In the present study, all these reported radiographic features in addition to the diagnostic potential of biochemical and clinical traits alongside radiologic attributes indicative of tumor severity were evaluated. By leveraging multivariable logistic regression model, the study demonstrated that simple biochemical and clinical factors like CA125, age, as well as CEA levels have the potential to effectively separate the diagnosis of both these tumors with good accuracy, implying clinical application. Moreover, the study revealed that models incorporating biochemical, clinical, and radiologic features either matched or surpassed the performance of radiology reports, echoing previous literature findings [25, 26].

Generalizability

It is possible to extrapolate the study's conclusions to comparable tertiary referral facilities with comparable patient demographics. Nonetheless, care must be used when extrapolating the findings to groups with unique clinical or demographic traits or other healthcare settings. To improve the generalizability of the findings, more validation through bigger, multi-center studies with a variety of patient groups is required.

Conclusion

The study of Krukenbergs tumor in MGM Medical College in Jharkhand, India sheds light on the diagnostic as well as prognostic aspects of Krukenberg tumors, by providing information into their clinical symptoms and therapeutic strategies. Despite the limitations inherent in a retrospective study from a single center, the findings emphasize the importance of considering various biochemical, clinical, and radiologic attributes to accurately distinguish Krukenberg tumors from ovarian cancers. While radiographic findings alone might not aid in accurate diagnosis, the incorporation of clinical and biochemical markers such as CA125, age, and CEA levels demonstrates promising results in terms of improved diagnostic accuracy. Moreover, this study highlights the need for larger, multicenter studies to validate and refine diagnostic as well as treatment approaches proposed in this study. The understanding of Krukenberg tumors is therefore crucial for optimization of the patient care as well as outcomes in the clinical scenario.

Limitations

The study is constrained by its retrospective design involving only a single-centre and excessive reliance on radiographic reports to get the tumor characteristics. Additionally, the smaller cohort might not be an adequate representative set for patients from different demographics.

Recommendations

The research suggests carrying out more extensive, multi-center prospective investigations to verify the results and enhance their generalizability. Furthermore, adding genetic profiling data and standardizing radiology reporting procedures may improve diagnostic precision.

Acknowledgement

The authors acknowledge and extend their heartfelt appreciation to all the participants for their cooperation.

List of Abbreviations

CT – Computed Tomography

IQR – Interquartile Range

CEA - Carcinoembryonic Antigen

KRAS - Kirsten rat sarcoma viral oncogene homolog

BRAF – Raf murine sarcoma viral oncogene homolog B

HER2 - Human Epidermal Growth Factor Receptor 2

OS – Overall Survival

PFS – Progression- Free Survival

Source of funding

No funding received.

Conflict of interest

The authors have no competing interests to declare.

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e-ISSN: 2709-9997, p-ISSN: 3006-1059
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https://doi.org/10.51168/sjhrafrica.v5i3.1103
Original Article

Publisher details

SJC PUBLISHERS COMPANY LIMITED

Catergory: Non Government & Non profit Organisation
Contact: +256 775 434 261 (WhatsApp)
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Website: https://sjpublisher.org
Location: Scholar's Summit Nakigalala, P. O. Box 701432,Entebbe Uganda, East Africa