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Determinants Of Complete Pathological Response Following Neo-Adjuvant Chemotherapy Among Breast Cancer Patients In A Tertiary Hospital In Ghana

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Abstract

Background

The wide-ranging features of breast cancer presents a challenge in accurate prognostication of the disease. There is a recent shift towards investigating pathological complete response(pCR) of surgical specimen following neo-adjuvant chemotherapy. However, there is dearth of information on such works in Ghana. This study sought to evaluate the determinants of complete pathological response in breast cancer patients who underwent surgery following neo-adjuvant chemotherapy at Komfo Anokye Teaching Hospital

Method

The study was a retrospective hospital-based study that included breast cancer patients who had neo-adjuvant chemotherapy and breast surgery between January 2021 to June 2023. Data collected included age, laterality, BMI, Histologic type and Grade, ER/PR/ HER-2 receptor status and final post-surgery pathological stage. Intrinsic subtype classification was performed according to the 2011 St Galen consensus.

Results

In the present study, the age distribution of malignant breast diseases showed a bimodal pattern. Invasive ductal carcinoma with no special type (IDC-NST) was the predominant histological type (85.5%). Triple-negative breast cancer formed the majority (46%) based on the immunohistochemical intrinsic subtype. A third of the study participants were at stage IIIB of the disease. A quarter of those who underwent neo-adjuvant chemotherapy before surgery achieved a complete pathological response. A multivariate analysis showed that patients who received 3 weekly doses of docetaxel had higher odds [OR: 2.94, p = 0.038] of achieving a complete pathological response. However, there was no significant difference between 3 weekly paclitaxel and weekly paclitaxel. Similarly, patients who received Herceptin as part of their neo-adjuvant treatment were more likely to have a complete pathological response [OR: 4.68, p = 0.023] in this study.

Conclusion

The clinicopathological features of breast cancer patients, along with neo-adjuvant therapeutic agents, can help predict complete pathological response and predict overall survival

INTRODUCTION

The broad range of clinicopathologic features of breast cancer makes it difficult to accurately predict the disease's prognosis [1]. Recently, there has been a growing focus on assessing pathological complete response (pCR) in surgical specimens after neoadjuvant chemotherapy as a way to predict survival and locoregional recurrence[2], [3].

Neoadjuvant chemotherapy (NACT) is a part of primary treatment for locally advanced breast cancer worldwide [4]. NACT has demonstrated excellent results in reducing tumor size, significantly increasing the number of patients eligible for breast-conserving surgery (BCS) and enabling surgery on otherwise inoperable breast tumors[5], [6]. In addition to the clinical benefits of tumor downstaging, neoadjuvant therapy also allows the monitoring of treatment response to chemotherapy agents, which could lead to adjustments in the treatment regimen tailored to individual patients [7].

While some authors define complete pathological response as ypT0/is + ypN0, others use ypT0ypN0 in their analysis [3]. Some researchers even focus solely on axillary pathological response [8]. Achieving a complete pathological response depends on several factors, such as the chemotherapy regimen used and the intrinsic subtypes. Some studies have reported pCR rates ranging from 18% to 34%[4], [9], [10]. The rate of complete pathological response in axillary disease after NACT ranges from 13% to 60%, depending on the intrinsic subtype of the disease [8].

According to Clegg-Lamptey et al., 2007, a three-year study conducted at the Korle-Bu Teaching Hospital found that out of 134 patients with invasive ductal carcinoma, 77 underwent NACT, and 6.5% of them achieved pCR [11]. A similar study from Kumasi showed that out of 31 patients, 23.2% achieved pCR after NACT [12]. The current study aims to evaluate the predictors of complete pathological response in patients with breast cancer who have undergone neo-adjuvant chemotherapy and surgery.

METHODS AND MATERIALS

This was a hospital-based retrospective study conducted at Komfo Anokye Teaching Hospital. The study population included patients who underwent breast surgery for malignant breast disease from January 2020 to December 2023. Ethical approval from the Institutional Review Board at Komfo Anokye Teaching Hospital (KATH IRB/AP/010/25).

Patients with core-biopsy-confirmed malignant breast lesions who underwent staging investigations discussed at a Multidisciplinary Team meeting, and who were offered neoadjuvant chemotherapy, were included in the study. Individuals with metastatic breast disease were excluded. Involved patients were offered either upfront surgery or neoadjuvant therapy. Those who underwent upfront surgery were also excluded.

Data were obtained from the electronic medical records and a structured questionnaire that included sections on age, laterality of the breast involved, histology of the breast lesion, immunohistochemistry status of the breast lesion, tumor stage (size), nodal status, neoadjuvant regimen received, type of surgery performed, and the pathological stage of the surgical specimen. Complete pathological

response was defined as pTo/pTis and pNo. Clinical stage was determined based on tumor size, nodal stage, and results from staging investigations according to the AJCC classification.

Data was analyzed using Stata/MP 14. Inferential analysis was performed with chi-square for categorical data and t-test for numerical outcomes. Multivariate logistic regression was used to predict complete pathological response following neoadjuvant therapy. A 95% confidence interval was reported for means and odds ratios, and a p-value < 0.05 was considered significant.

RESULTS

During the study period, 256 patients underwent breast surgery for malignant breast disease, including one male patient. The patients' ages ranged from 26 to 88 years, with a mean age of 51.9 (± 12.0) years. The data showed a bimodal pattern, with peaks in the early 40s and late 50s. The average BMI of the population was 28.5 (± 10.6) kg/m².

Within the study period, the most common breast malignant lesion diagnosed was invasive ductal carcinoma, no-special type. This was observed in 88.9% of the study population. Other histologic types of breast cancer include lobular carcinoma (9), papillary carcinoma (3), and colloid carcinoma (6).

Triple negative breast cancer accounted for 45.5% of the intrinsic histologic subtypes. It was followed by Luminal A breast cancer (33.6%), non-luminal Her2-positive (14.5%), and Luminal B (6.4%).

At presentation, 26.9% had stage IIIA breast cancer, 44.7% had stage IIIB breast cancer, while 10.6% had stage IIIC. 13.5% had stage IIB. Only 3.3% and 1% had stage IIA and stage I, respectively. Among the patients who underwent breast surgery for malignant breast disease, only 8% underwent breast-conserving surgery.

208 patients underwent neo-adjuvant chemotherapy before surgery. After treatment with Adriamycin and cyclophosphamide, the additional neo-adjuvant chemotherapy regimens included 3-weekly docetaxel (46%), 1-weekly paclitaxel (25%), 3-weekly paclitaxel (20%), and 1-weekly carboplatin plus paclitaxel (5%). Less than 5% received 1-weekly docetaxel, 3-weekly carboplatin plus docetaxel, epirubicin, methotrexate, or 5-fluorouracil. Twenty out of fifty patients with Her2/neu receptor positivity received neo-adjuvant targeted therapy (trastuzumab) in addition to chemotherapy. Two patients received only hormonal therapy as neo-adjuvant treatment.

A quarter of all patients who underwent neo-adjuvant chemotherapy before surgery achieved complete pathological response. Table one shows characteristics of patients who achieved complete pathological response after neo-adjuvant chemotherapy.

Table 1
Characteristics of Patients Who Achieved Complete Pathologic Response

	pCR			
	Yes(n = 52)	**No(n = 156)**	**Total**	**P-value**
Age[95 CI] years	49.5[46.4–52.6]	52[50.0–54.0]	51.4[49.7–53.0]	0.169
Stage I	0	2	2	0.117
Stage IIA	2	5	7	
Stage IIB	8	20	28	
Stage IIIA	21	35	56	
Stage IIIB	17	76	93	
Stage IIIC	4	18	22	
Luminal A	14	53	67	0.533
Luminal B	5	10	15	
Non-Luminal Her 2+	11	23	34	
Triple Negative	22	70	92	
Left	23	69	92	0.933
Right	29	87	116	
IDC-NST	48	137	185	0.36
Lobular carcioma	4	7	11	
Papillary carcinoma	0	4	4	
Colloid carcinoma	0	8	8	
Only AC	1	1	2	0.684
AC + 1w CP	3	8	11	
AC + 1w P	10	42	52	
AC + 3w CD	0	1	1	
AC + 3w D	29	67	96	
AC + 3w P	9	35	44	
AC + Hormonal	0	2	2	
BCS	2	6	8	

	pCR			
	Yes(n = 52)	**No(n = 156)**	**Total**	**P-value**
MRM	50	150	200	

From Table 2, patients who received 3 weekly docetaxel had higher odds [OR: 2.94, p = 0.038] of achieving complete pathological response. There was no difference between 3 weekly paclitaxel and weekly paclitaxel. Similarly, patients who received targeted therapy as part of neoadjuvant treatment were more likely to have a complete pathological response [OR: 4.68, p = 0.023].

Table 2
Multivariate analysis of predictors of Complete Pathological Response

COMPLETE PATHOLOGICAL RESPONSE(+ pTis)			
	ODDS RATIO	**CI 95**	**p-value**
LUMINAL A	0.94	0.23–3.94	0.938
LUMINAL B	0.93	0.14–6.35	0.942
NON-LUMINAL HER2	0.86	0.15–4.78	0.863
TRIPLE NEGATIVE	1.04	0.26–4.17	0.954
3-WEEKLY DOCETAXEL	2.94	1.06–8.14	**0.038**
3-WEEKLY PACLITAXEL	1.63	0.48–5.50	0.435
WEEKLY PACLITAXEL	1.74	0.54–5.60	0.351
WEEKLY CARBOPLATIN+PACLITAXEL	3.63	0.71–18.58	0.122
TARGETED THERAPY (TRASTUZUMAB)	4.68	1.24–17.68	**0.023**

DISCUSSION

In the present study, the participants' age distribution showed a bimodal pattern, peaking in the early 40s and late 50s. Seshie et al. also found that the age at diagnosis for breast cancer was bimodal, with peaks in the early 40s and early 60s [1]. The average age of our study population was 51.9 (± 12.0) years, which is similar to that reported by Seshie et al.: 52.5 (± 12.1) years [1]. Other studies in Ghana have shown that the average age of breast cancer patients at diagnosis is younger than what we observed. Awoonor-Williams et al. [12] and Clegg-Lamptey et al. [11] reported mean ages of 47.68 (± 10.05) and 48.1 years, respectively. Unlike this study, Clegg-Lamptey et al. reported a single peak in the early 40s [11]. In the United States, it has been observed that the peak age of diagnosis for white women is in the early 7th decade, while for non-white women, it is in the 5th decade [13].

As observed in this study, the overwhelming majority of histologic breast cancer types were invasive ductal carcinoma, no-special type (IDC-NST). This aligns with other studies conducted both locally and internationally, where the proportion of IDC-NST often accounted for more than 80% of all histologic breast cancer types [11], [12], [14]. The majority of the cases were at the advanced stage of the disease owing to the poor health-seeking behavior of most Ghanaians. This agreed with a comparative study by Stark et al, where most of the Ghanaian participants had a more advanced form of the disease than African Americans and Americans[15]. An earlier study in Ghana has shown that the average tumour size at presentation is 6-7cm. In that study, it was found that 45.2% of patients presented with peau d'orange or breast ulceration [11].

In this study, triple-negative breast cancer was the most common intrinsic subtype, followed by Luminal A breast cancer, non-luminal HER2-positive, and Luminal B. This sequence is the same as reported in similar studies from Ghana [1], [12]. Siddharth et al. reported that TNBC accounts for 15–20% of all breast cancers globally, a proportion lower than that observed in our study [16]. The incidence of triple-negative breast cancer is notably higher in women of African descent (27%) [17]. According to Hercules et al. [17], among Africans, women from West Africa have an even higher proportion of TNBC [45.7% (95% CI: 38.8% – 52.8%), I^2 = 91]. Some studies have reported TNBC proportions of 61% and 82% in the Ghanaian population, considerably higher than the 46% we found in this study[15], [16].

In our study, only 3.8% of patients who received neoadjuvant chemotherapy underwent breast-conserving surgery. This is partly due to the late presentation of most patients. The proportion of BCS for breast cancer in our study is significantly lower than what Nsaful et al. reported. In their study, about a quarter of the patients had BCS. However, compared to this study, more patients presented with early-stage breast cancer [18]. Again, a study conducted in South Africa showed that 20.4% of all patients undergoing breast surgery for cancer had BCS. However, considering patients who had neoadjuvant chemotherapy before surgery, only 6% had BCS, which is closer to what we found in this study [19]. A systematic review by Gu and colleagues showed a decreasing rate of BCS with higher clinical stage [20].

In our study, one-quarter of patients who received neoadjuvant chemotherapy achieved a complete pathologic response in the surgical specimen. The pathologic complete response rate by intrinsic subtype was 20.9%, 33%, 32%, and 23.9% for Luminal A, Luminal B, Non-luminal HER2, and TNBC, respectively. In a similar study conducted in France, the overall pCR rate among 1212 participants was 18%. The breakdown of intrinsic subtypes showed that the pCR rate was 7.5% in luminal A, 15% in luminal B/HER2-negative, 22% in luminal B/HER2-positive, 36% in HER2-positive/non-luminal, and 31% in triple-negative breast cancer [2]. Greenwell et al. reported that 38.8% of their HER2-positive breast cancer patients achieved pCR following neoadjuvant chemotherapy [9]. This figure is closer to the 32% observed in our study among HER2-positive breast cancer cases.

Similar to this current study, Candas et al. reported an overall pCR of 28.5%. However, the major difference they found compared to this study is a very high pCR rate among non-Luminal HER2 breast cancer patients (85.2%), while Luminal A patients had significantly lower pCR (6.8%) [10]. Unlike this

study, other researchers have reported a much higher pCR rate in TNBC. Gass et al. reported pCR rates of 41.8% and 50%, depending on the NACT regimen [21]. Similar to Gass et al. and different from the present study, Chen and colleagues found that out of 112 patients with early-stage triple-negative breast cancer, 49.1% achieved complete pathological response [22].

In this study, multivariate regression analysis showed that patients who received 3-weekly docetaxel had significantly higher odds of achieving a pathological complete response (pCR) [OR 2.94, p = 0.038]. This finding contradicts work published by Zhi-Dong et al., who observed that a paclitaxel-containing neo-adjuvant regimen resulted in a higher proportion of pCR compared to docetaxel [23]. Other studies have also found no difference in the pCR rate between docetaxel and paclitaxel. While some research found no difference between platinum and non-platinum containing NACT [24], as seen in this study, Dieci et al. reported that a carboplatin-containing regimen has 2.4 times higher odds of resulting in pCR compared to carboplatin-free NACT [25].

In this study, there was no difference in pCR rates between patients who received weekly and 3-weekly paclitaxel. This finding contradicts a similar study from Bangladesh, where patients who received weekly paclitaxel had significantly higher pCR rates compared to those in the 3-weekly group [26]. Although weekly paclitaxel has been reported to yield better outcomes than 3-weekly paclitaxel, it has also been observed that 3-weekly paclitaxel has a worse adverse profile [27].

Finally, our study demonstrated that targeted therapy (trastuzumab), as part of a neoadjuvant regimen, was associated with higher rates of pathological complete response (pCR). This finding is consistent with other studies that have demonstrated that the addition of trastuzumab to neo-adjuvant chemotherapy significantly increases the rate of pCR, regardless of ER status [28].

CONCLUSION

Neo-adjuvant chemotherapy plays a crucial role in the management of locally advanced breast cancer. Clinicopathological features, in addition to the choice, dosing, and scheduling of neo-adjuvant chemotherapy, are among the contributing factors that determine complete pathologic response in Ghanaian women.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Komfo Anokye Teaching Hospital (KATH IRB/AP/010/25). As this was a retrospective study using de-identified patient records, the requirement for individual informed consent was waived by the IRB.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

JS - conception, design of the work, analysis, and interpretation of data, manuscript draftIK - conception, design of the work; interpretation of data; drafting and revision of manuscriptSM - conception, design of the work, substantively revised manuscriptAAP - conception, design of the work; acquisition and interpretation of data; substantively revised manuscriptJA - acquisition, analysis, and interpretation of data, substantively revised manuscriptEO -acquisition, analysis, and interpretation of data; substantively revised manuscriptCO - acquisition, analysis, and interpretation of data, substantively revised manuscript

Data Availability

All data supporting the findings of this study are available upon request

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Figures

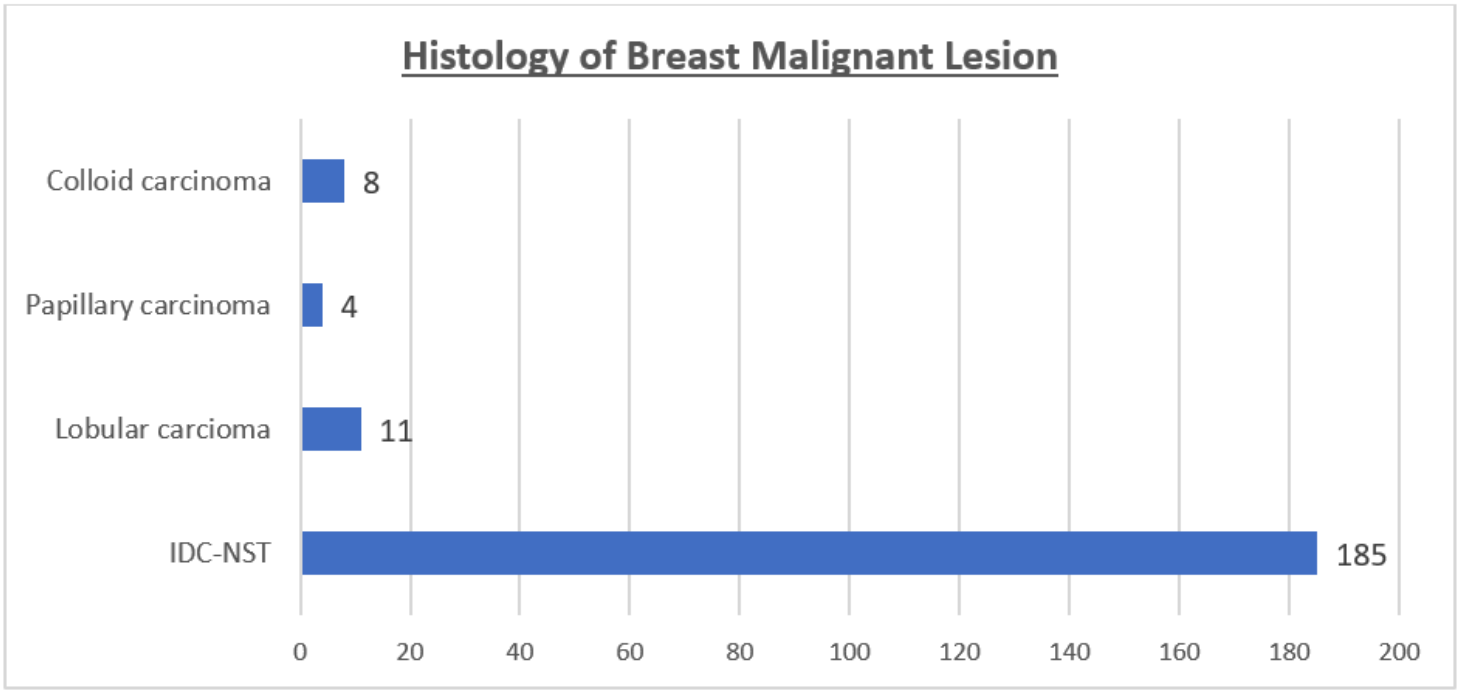


Figure 1

Legend not included with this version

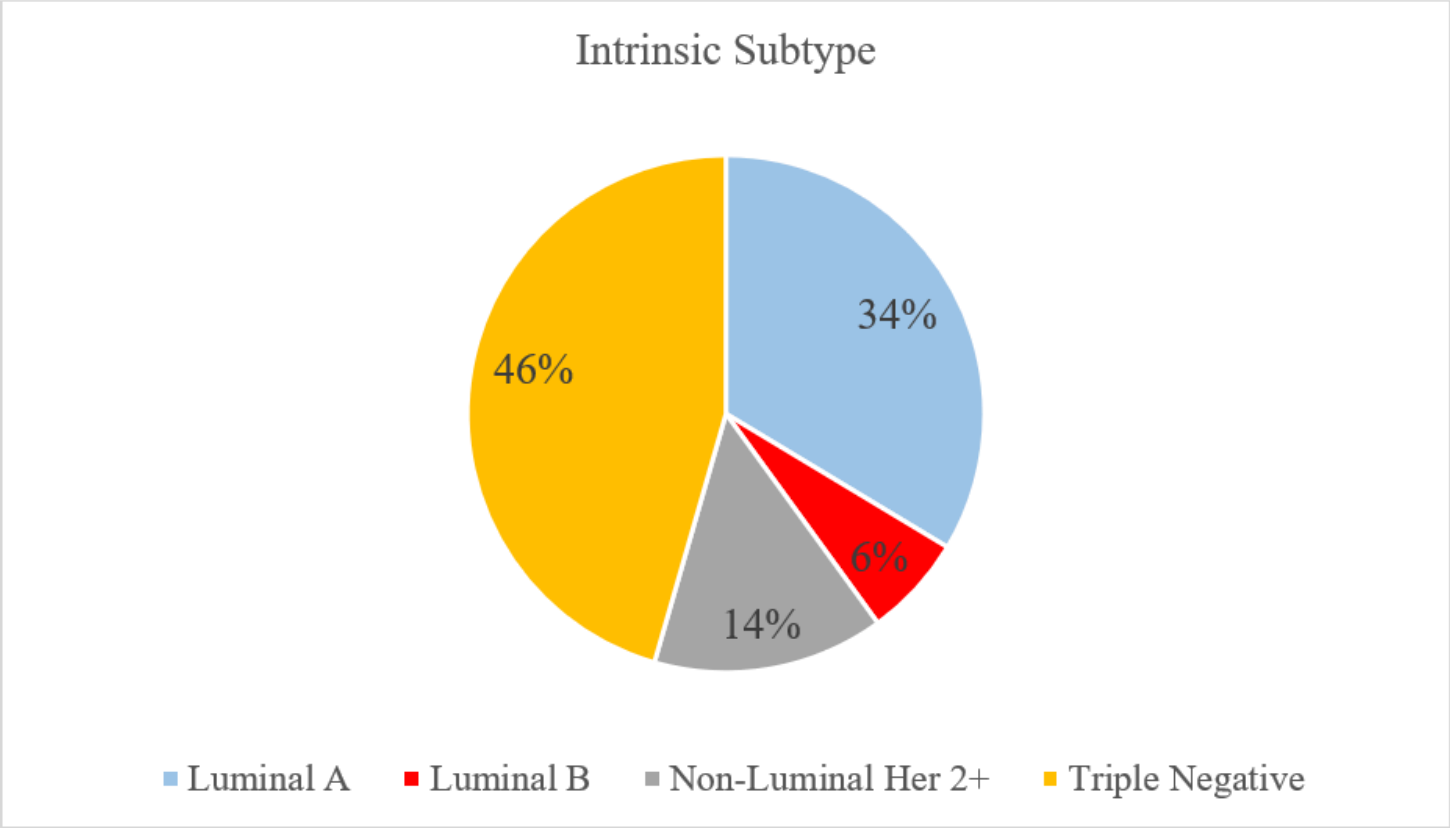


Figure 2

Intrinsic Subtype of Breast Cancer

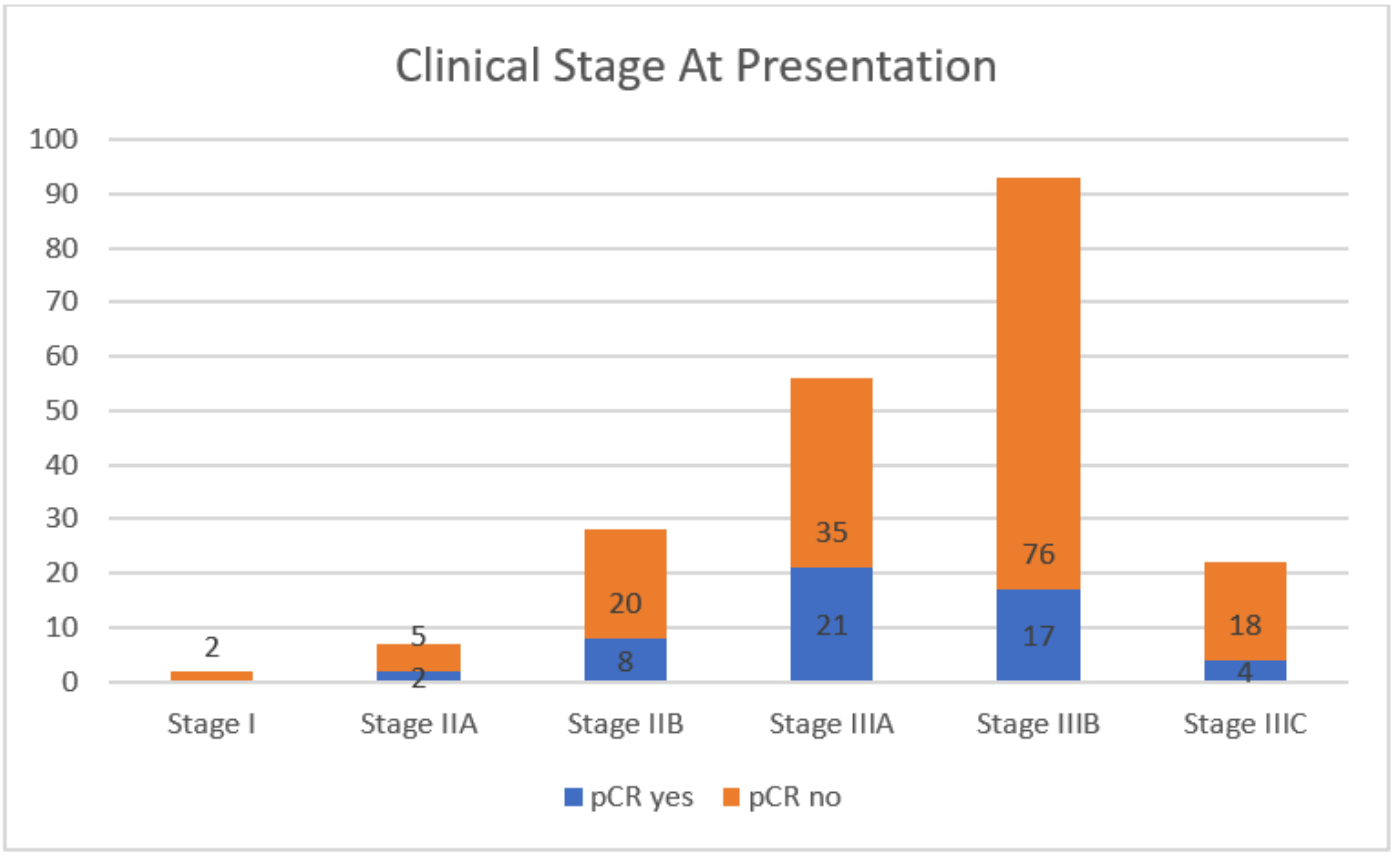


Figure 3

Clinical Stage at Presentation