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REVIEW

Effect of time to breast cancer surgery after neoadjuvant chemotherapy on survival outcomes

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Abstract

Background Neoadjuvant chemotherapy (NACT) is a cornerstone in managing breast cancer. There is no defined consensus on the optimal time between NACT and surgery. We analyze the effect of time between the end of NACT and surgery on overall survival (OS) and disease-free survival (DFS) in breast cancer patients who received NACT followed by surgery.

Methods This is a retrospective analysis of 468 patients with breast cancer (stage I–III) who received and completed the same regimen of NACT (Anthracyclines and Taxanes B27 protocol) at King Hussein Cancer Center (KHCC) (2006–2014). Patients have been divided into three groups according to the duration between the end of NACT and surgery, <4 weeks, 4–8 weeks and >8 weeks.

Results Most patients were stages II–III breast cancer with only four patients with stage I. Almost all patients (99%) had either invasive ductal or invasive lobular carcinomas. Adjuvant radiotherapy was given to 96% of patients. Most patients were alive at the time of analysis (84%).

Complete pathological response was achieved in 20% of patients. Local recurrence rate was 6.6% with a median follow up of 3.8 years (interquartile range 0.6–10.9). Analysis showed that the groups had equivalent DFS. However, OS was adversely affected if patients had their surgery after 8 weeks of NACT compared to those who had their surgery between 4 and 8 weeks.

Conclusions Breast cancer surgery post NACT within the first 8 weeks had no impact on survival. However, surgery after 8 weeks of NACT showed negative impact on OS. Therefore, delaying surgery after 8 weeks is not recommended.

Keywords Neoadjuvant therapy · Breast cancer · Breast surgery · Oncology · Chemotherapy

Introduction

The utilization of neoadjuvant chemotherapy (NACT) in breast cancer has been well established, especially after randomized controlled trials showing equal outcomes in survival compared to adjuvant chemotherapy [1, 2]. Not only did NACT allow downsizing the tumor in a group of patients who were otherwise not suitable for breast conservation [3], it also assisted in testing the tumor biology in vivo which allowed the evaluation of systemic therapy effects and tumor response. Furthermore, it has also allowed downstaging the clinically positive axilla in exceptional responders, thus performing less morbid surgeries [4, 5].

In Jordan, breast cancer is the most common cancer and the leading cause of cancer-related mortality in women, comprising 19.7% of all diagnosed cancer cases [6]. Moreover, about a third of patients present with locally advanced and or metastatic disease at a median age of 50, which is about a decade earlier than in the west. This makes the use of NACT more paramount in our population [7, 8]. The B-27 protocol (anthracycline taxanes) NACT has been used in our Jordanian patients with established efficacy and safety [9].

Limited data is available regarding the optimal timing to perform surgery after completing NACT, and major studies that addressed this issue showed contrasting results [10–13]. However, several published studies investigated the suitable time to initiate adjuvant chemotherapy, which lead several bodies of oncology to propose not delaying systemic adjuvant chemotherapy more than 6 weeks post-surgery [14–19].

In this retrospective comparative study, we aim to find the optimal time between completing NACT and having the

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surgery in relation to disease-free (DFS) and overall survival (OS).

Methods

Patient population

A retrospective chart review of 468 patients treated with NACT followed by surgery at King Hussein Cancer Center (KHCC) between 2006 and 2014. All patients had pathologically proven breast cancer, who received and completed the same regimen of NACT (B27 protocol [1]). Anti-Her2 agent (Trastuzumab) was added if the patients were eligible. Patients with de novo metastasis were excluded. Time to surgery was defined as the duration between the last cycle of NACT and the date of tumor removal. All patients were discussed in our specialized breast cancer multidisciplinary meeting, where recommendations were reached based on mammograms, histology and clinical presentation.

The study was conducted at KHCC Amman, Jordan, approved by the Institutional Review Board (IRB) with approval Number (17 KHCC 49).

Operative technique

All patients who underwent curative surgery were included in our analysis irrespective of the surgical technique involved.

Data collection and follow up

Patient demographics and medical histories were extracted pre-chemotherapy. We followed up with our patients with six monthly mammograms for 2 years and then every year thereafter and an annual computed tomography chest/abdomen/pelvis for 5 years.

Patients were divided into three groups according to the time to surgery: group 1: <4 weeks; group 2: 4–8 weeks; and group 3: >8 weeks. DFS and OS were calculated from the date of diagnosis to the date of recurrence or death, respectively.

Statistical analysis

Patients' characteristics such as histology, stage and hormone status were presented in terms of counts and percentages. Duration between NACT and surgery was divide into three sequenced ranges based on ROC optimal thresholds and AUC. Accordingly, duration between NACT and surgery (<4, 4–8 and ≥8 weeks) was compared using Chi-square test, Fishers exact or Wilcoxon rank as appropriate and based on each assumption. DFS and OS were presented by Kaplan Meier curves and the comparisons were performed using Log Rank test. Significant factors were included in Cox regression and Adjusted Hazards ratios, their 95% CI and Adjusted p values were reported. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

The analysis included 468 patients who underwent NACT followed by surgery between 2006 and 2014. Seventy-five patients (16%) were dead at the time of the analysis. Complete pathological response was achieved in 20% of patients, the local recurrence rate was 6.6% ($n=31$) and the distant metastasis rate was 22% ($n=102$). Median follow up for the whole cohort was 46 months (interquartile range 7–131). There were 142 patients in the <4 weeks group, 284 patients in the 4–8 weeks group, and 42 patients in the >8 weeks group. Their clinical characteristics are shown in Table 1. The three groups were not statistically different regarding age, cancer histology, grade, hormonal receptor status, the use of adjuvant hormonal or radiotherapy or the pathologic complete response (pCR). And the <4 weeks groups had more percentage of patients with lymphovascular invasion (LVI) ($p<0.03$) and long duration of follow up (median) 4.6 years with ($p=0.022$) and the >8 weeks group had fewer patients who initially presented with stage III breast cancer ($p<0.0001$).

The 5-year survival rates were 89%, 77%, and 85.6% for the groups <4 weeks, 4–8 weeks and >8 weeks, respectively. The Kaplan Meier curves for OS and DFS for all groups are shown in Figs. 1 and 2.

In the univariable analysis, Table 2, TNM clinical and pathological stage, LVI, nuclear grade, pathological response and Hormonal receptor status affected DFS. Whereas time to surgery, TNM clinical and pathological stage, LVI, nuclear grade and Hormonal receptor status were statistically significant factors for OS. Breast reconstruction did not have an influence on DFS nor OS.

In the multivariate Cox regression, Table 3, only the presenting clinical stage (III vs. I/II) and LVI were shown to be associated with worse OS, whereas in DFS, grade, LVI and the clinical stage were shown to be significant detrimental factors. Time to surgery did not have an influence on neither DFS nor OS.

In comparing the groups' OS and DFS (Tables 4 and 5, respectively), patients who underwent surgery beyond 8 weeks post NACT had worse OS than the 4–8 weeks group.

Table 1 Patient characteristics

Variable	Value	All patients $n=468$ Number (%)	<4 weeks $n=142$ Number (%)	4–8 weeks $n=284$ Number (%)	>8 weeks $n=42$ Number (%)	p value
Age	≤50	306 (65.4%)	98 (32.0%)	182 (59.5%)	26 (8.5%)	0.53
	>50	162 (34.6%)	44 (27.2%)	102 (63.0%)	16 (9.9%)	
Histology	IDC[a]/ILC[b]	452 (97%)	137 (30.3%)	274 (60.6%)	41 (9.1%)	0.75
	Others	16 (3%)	5 (31.3%)	10 (62.5%)	1 (6.3%)	
Grade	I/II	228 (49%)	66 (28.9%)	140 (61.4%)	22 (9.6%)	0.71
	III	226 (48%)	73 (32.3%)	134 (59.3%)	19 (8.4%)	
	NA[c]	14 (3%)	3 (21.4%)	10 (71.4%)	1 (7.1%)	
Subtype	HR[d] +ve	321 (68.7%)	99 (30.7%)	195 (60.6%)	28 (8.7%)	0.929
	Her2 +ve	128 (27%)	33 (25.8%)	85 (66.4%)	10 (7.8%)	0.43
	TN[e]	43 (9.4%)	14 (32.6%)	26 (60.5%)	3 (7.0%)	0.80
Median follow-up (years)	Median	3.8	4.6	3.6	3.6	0.022
	IQR	(2.9–5.1)	(2.7–6.6)	(2.9–4.8)	(3.1–4.4)	
LVI[f]	Present	169 (36.1%)	60 (35.5%)	99 (58.6%)	10 (5.9%)	0.03
Radiotherapy	Yes	426 (91%)	131 (30.8%)	257 (60.3%)	38 (0.9%)	0.83
Clinical stage	I/II	191 (40.9%)	44 (23.0%)	121 (63.4%)	26 (13.6%)	0.0001
	III	277 (59.1%)	98 (35.4%)	163 (58.8%)	16 (5.8%)	
Path response	CR[g]	92 (19.7%)	22 (23.9%)	63 (68.5%)	7 (7.6%)	0.23
Path stage	CR[g]	92 (19.7%)	22 (23.9%)	63 (68.5%)	7 (7.6%)	0.11
	I/II	204 (43.6%)	56 (27.5%)	126 (61.8%)	22 (10.8%)	
	III	172 (36.8%)	64 (37.2%)	95 (55.2%)	13 (7.6%)	
Surgery type	BCS	120 (25.6%)	40 (33.3%)	72 (60.0%)	8 (6.7%)	0.49
	Mastectomy	348 (74.4%)	102 (29.3%)	212 (60.9%)	34 (9.8%)	
Breast reconstruction (mastectomy)	Delayed	5 (1.4%)	4 (80.0%)	1 (20.0%)	0 (0.0%)	0.13
	Immediate	106 (30.5%)	16 (15.1%)	79 (74.5%)	11 (10.4%)	
	No	237 (68.1%)	82 (34.6%)	132 (55.7%)	23 (9.7%)	
Radiotherapy (post-mastectomy)	No	41 (11.8%) 307 (88.2%)	10 (24.4%)	27 (65.9%)	4 (9.8%)	0.752
	Yes		92 (30.0%)	185 (60.3%)	30 (9.8%)	

[a]Invasive ductal carcinoma

[b]Invasive lobular carcinoma

[c]Not applicable

[d]Hormonal receptor

[e]Triple negative

[f]Lymphovascular invasion

[g]Complete response

Discussion and conclusion

This retrospective comparative study aims to study the effect of time of breast cancer surgery after NACT on patients' survival. Our data showed that when comparing patients who had surgery beyond 8 weeks to patients who had the surgery between 4 and 8 weeks, the former group showed worse OS. Also, when the >8 weeks group was compared to the combined cohort of <8 weeks post treatment, there was a statistical trend towards worse OS.

Scheduling patients who completed NACT for surgery is dictated by many factors; toxicity from chemotherapy, which was shown to be the major cause of delay to surgery [3], patients' medical status and anxiety can play a role in delaying surgery. In addition, operating theatre slot availability and surgical waiting lists might also be taken into consideration.

In the literature, there is no clear-cut evidence on the optimal time to perform the surgery post NACT.

A published study by Sanford et al. was the first to address this issue [10]. It was a retrospective review of 1101 patients diagnosed with stages I, II and III. Time between NACT and surgery was categorized as <4 weeks (30.4% of patients), 4–6 weeks (47.6%), or >6 weeks (22%). The 5-year OS estimate was 79%, 87% and 81% respectively ($p=0.03$). They did not find a difference between the three groups in terms of DFS. Patients who underwent surgery at ≤4 or >6 weeks had worse OS but not DFS.

Another study from Modena Italy showed a better OS and DFS outcome if surgery was performed before the

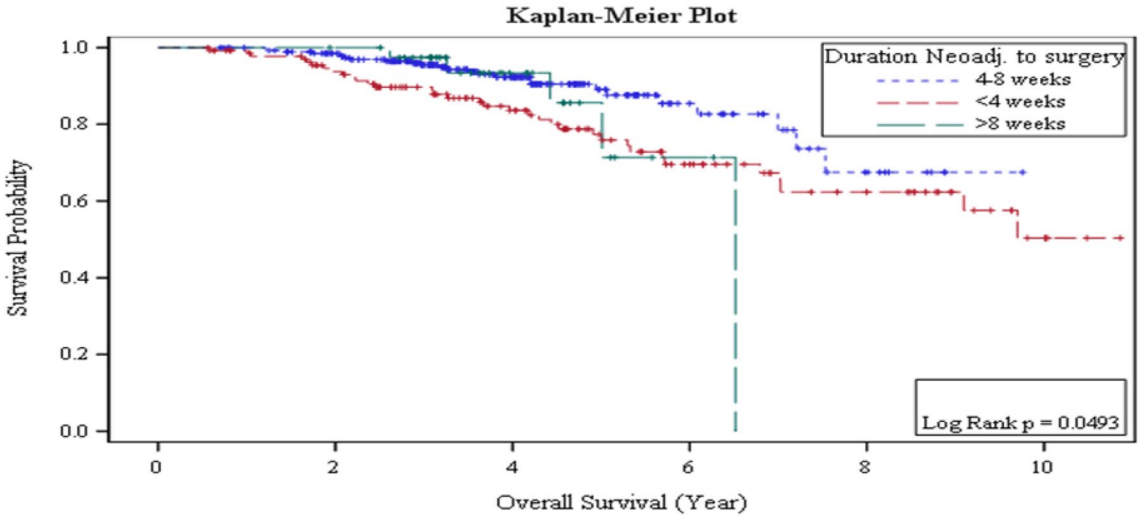

Fig. 1 The Kaplan Meier Plot for all patient groups' overall survival. Duration is between the neoadjuvant therapy and surgeryThe Kaplan Meier Plot for all patient groups' overall survival. Duration is between the neoadjuvant therapy and surgery

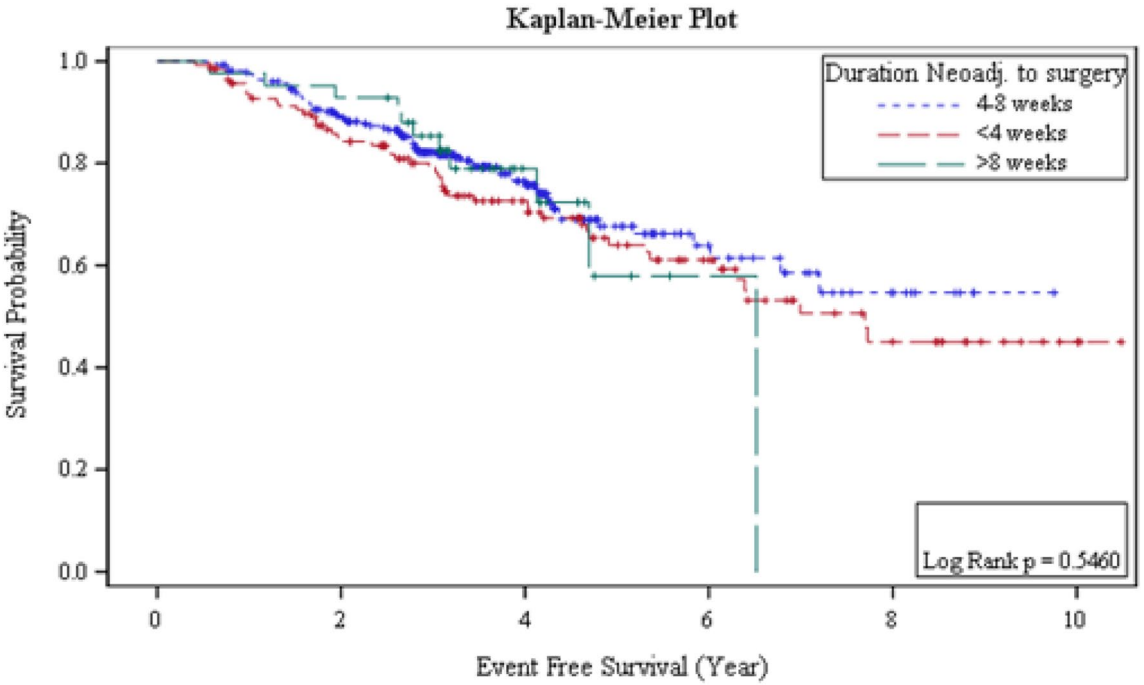

Fig. 2 The Kaplan Meier Plot for all patient groups' event free survival. Duration is between the neoadjuvant therapy and surgery

end of 3 weeks post treatment. However the groups were mismatched in number [11]. Authors from the Kaiser Permanente Los Angeles Medical Center conducted their own review on 58 patients and found that delaying surgery beyond 60 days affects recurrence but not survival [12].

As far as we know, this is the second analysis of its kind in our region, the Middle East, outside of Europe and the United States. One of our aims was to know if findings could be replicated in our specific cohort of patients.

The retrospective nature of this study may have an adverse impact on the outcome especially with a small sample size in the >8 weeks group. It is also a single center experience and overgeneralizing results should be taken with caution.

Table 2 Univariate analysis, disease free survival and overall survival

Variable		*N*	Disease free survival 5 Year estimate (CI 95%)	*p*-value	Overall survival 5 Year estimate (CI 95%)	*p*-value
Age	≤50	306	63.8 (56.5–70.7)	0.7029	83.6 (77.6, 88.9)	0.7135
	>50	162	71.8 (63.2–79.7)		87.2 (79.9, 93.0)	
Time to surgery	<4 weeks	142	64.0 (54.5–72.9)	0.5460	77.3 (68.6–85.0)	0.0493
	4–8 weeks	284	67.7 (60.0–74.9)		89.1 (83.4–93.7)	
	>8 weeks	42	57.9 (29.3–83.9)		85.6 (65.4–97.8)	
TNM clinical stage	1/II	191	85.4 (77.3–92.0)	<0.0001	93.0 (87.0–97.3)	0.0025
	III	277	55.0 (47.8–62.2)		79.8 (73.4–85.5)	
TNM path stage	CR	92	73.0 (56.5–86.7)	<0.0001	87.7 (77.1–95.4)	<0.0209
	I/II	204	76.0 (67.8–83.3)		87.4 (80.4–93.0)	
	III	172	52.8 (44.1–61.4)		80.6 (72.8–87.4)	
Pathological response (CR[a])		92	73.0 (56.5–86.7)	0.0102	87.7 (77.1–95.4)	0.1249
Subtype	HR[b] +ve	322	69.7 (63.1–76.0)	0.0278	87.4 (82.2–91.9)	0.0312
	HER2 +ve	128	68.7 (57.4–78.9)	0.3095	82.3 (71.5–90.9)	0.612
	TN[c]	44	60.7 (40.8–78.9)	0.2381	83.7 (69.6–94.0)	0.5868
Surgery type	BCS	120	75.1 (64.5–84.4)	0.0326	93.0 (86.3–97.5)	0.0828
	Mastectomy	348	63.0 (56.3–69.6)		81.7 (75.8–87.0)	
Grade	I, II	228	72.3 (64.6–79.4)	0.0137	88.6 (82.7–93.4)	0.047
	III	226	59.0 (50.2–67.5)		80.1 (72.2–87.0)	
	NA[d]	14				
LVI[e] present		169	51.9 (42.7–61.0)	<0.0001	74.8 (65.8–82.9)	0.0003
Radiotherapy (post-mastectomy)		307	66.5 (60.7–72.1)	0.9978	85.0 (80.2–89.2)	0.7153
Breast reconstruction (mastectomy)	Delayed	5	80.0 (38.5–99.9)	0.2236	80.0 (38.5–99.9)	0.1349
	Immediate	106	68.2 (55.8–79.4)		91 (82.6–96.8)	
	No	236	60.1 (55.8–79.4)		77.7 (69.8–84.8)	

[a]Complete response

[b]Hormonal receptor

[c]Triple negative

[d]Not applicable

[e]Lymphovascular invasion

Table 3 Multivariate Cox regression analysis showing overall survival and disease-free survival of all patients

	Overall survival *p* value	Disease free survival *p* value
Duration	0.1108	0.2302
Grade	0.1696	**0.0166**
Estrogen receptor	0.1153	0.0999
Clinical stage	**0.0373**	**0.0011**
Path stage	0.4352	0.5499
Lymphovascular invasion	**0.0023**	**0.0001**

Table 4 A comparison between the overall survival between patient groups

Hazard ratio (HR)	*p* Value	Duration
<4 weeks vs. 4–8 weeks	0.2848	1.392
>8 weeks vs. 4–8 weeks	**0.0442**	2.851
>8 weeks vs. <8 weeks	0.0667	2.519
>8 weeks vs. <4 weeks	0.7757	1.155

Duration is between the neoadjuvant therapy and surgery

Theoretically to define the optimal time post NACT to surgery, prospective randomized trials are needed which are perhaps very difficult to conduct as they may harbor ethical issues.

With the limited data available on the subject, delaying surgery up to 8 weeks does not impact outcomes and this might give surgeons reassurance regarding scheduling their patients for surgery.

Table 5 A comparison between disease free survival among patient groups

Duration	*p* value	Hazard ratio (HR)
<4 weeks vs. 4–8 weeks	0.6514	0.908
>8 weeks vs. 4–8 weeks	0.1252	1.718
>8 weeks vs. <8 weeks	0.3390	1.359
>8 weeks vs. <4 weeks	0.3924	1.349

Duration is between the neoadjuvant therapy and surgery

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Data availability The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest MA-M declares that he has no conflict of interest. BA declares that he has no conflict of interest. HA-N declares that he has no conflict of interest. TA-S declares that he has no conflict of interest. No funding to declare, the authors are employed at KHCC where this research was carried out.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board (IRB) at King Hussein Cancer Center (KHCC) with IRB approval # 17KHCC49.

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