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AWAKE BREAST SURGERY AND DE-ESCALATION TREATMENT: STRATEGIES FOR FRAIL AND ELDERLY BREAST CANCER PATIENTS

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ABSTRACT – ***Objective:*** Awake breast surgery has been proven to be a concrete alternative to surgery under general anesthesia. This technique was shown to be advantageous in various aspects such as length of hospitalization and economic sustainability. Our study aims to verify the advantages of this technique in terms of operating room times, length of stay, and outcome in frail patients diagnosed with breast cancer.

Patients and Methods: Our retrospective study enrolled all frail patients, ASA ≥ 3, diagnosed with breast cancer and scheduled to undergo a surgical intervention. The type of surgery, duration of surgery, length of hospital stay, type of anesthesia, postoperative complications, postoperative dissociative episodes and CCI (Charlson Comorbidity Index) score were evaluated by comparing the data between the group of awake surgery and the group of patients undergoing surgery under general anesthesia.

Results: A total of 34 patients were enrolled; 16 patients (45.7%) undergoing awake surgery with a mean age of 78 years [75;95], and 18 patients (54.3%) receiving general anesthesia. CCI was significantly higher in the Awake group with a median score of 12 [9;13] *vs.* 10 [9;11] in the No-Awake group: relative *p*-value was <0.001. Postoperative complications were comparable between the groups, showing no statistically significant differences. Six patients (33.3%) in the general anesthesia group experienced dissociative complications *vs.* 1 (6.3%) in the awake surgery group (p=0.05). There were no statistically significant differences regarding the other parameters.

Conclusions: PAwake breast surgery in elderly patients, especially in frail ones, could reduce the incidence of postoperative delirium by enabling a shorter hospitalization and allowing for a faster recovery.

KEYWORDS: De-escalation, Breast cancer surgery, Awake breast surgery, Elderly.

INTRODUCTION

Ageing remains one of the most important risk factors for breast cancer development[1]. More than 30% of newly diagnosed breast cancers occur in elderly patients[2]. Increasing life expectancy, especially among the western world population, has been associated with an increase of breast cancer in older women[1]. Elders are more frequently frail patients with higher comorbidity and increased anesthesiologic risk, further complicating cancer treatment choice[3]. In fact, in elder women, breast cancer management remains challenging for clinicians who do not have at their disposal all the available treatment options[2]. There is no agreement regarding the optimum treatment in elderly patients[4,5]. Breast cancer in elderly patients apparently presents with favorable prognostic factors, such as low grade, reduced incidence of lymph nodes invasion, and higher estrogen-receptor overexpression[3,6-8]. Despite these and due to the possible side effects associated with the treatment, elderly patients often receive less than standard of care[9]. Axillary surgery, adjuvant chemotherapy and/or radiotherapy are frequently omitted[10,11]. In elderly patients, especially with elevated anesthesiologic risk (ASA), surgery could substitute primary hormone therapy or radiotherapy [10].

Surgery in elderly patients seems to be associated with an improvement in terms of breast cancer survival and disease-free survival, with a lower morbidity despite the anesthesiologic risk[12,13]. Awake breast surgery is an effective strategy for reducing the anesthesiologic risk and surgical operative morbidity[14,15]. The aim of this retrospective study is the evaluate the feasibility and outcomes of awake breast surgery in frail elder patients with an elevate anesthesiologic risk.

PATIENTS AND METHODS

All female patients aged ≥75 years old with an ASA≥3 subjected to breast surgery between January 2017 to December 2018 at the Breast Unit of the University of Rome Tor Vergata were evaluated in this retrospective study. The retrospective manuscript was approved by the institutional review board.

Awake breast surgery included all procedures with administration of local anesthetics or loco-regional anesthesia without mechanical ventilation, with or without mild sedation Richmond agitation-sedation scale ≥-4. This group was designated as Awake group. Otherwise, patients under general anesthesia and mechanical ventilation using glottic or supra-glottic devices were included in the control group (No-Awake group). Age, BMI, ASA score and Charlson Comorbidity Index (CCI) were collected from clinical notes and evaluated in the study. Surgical procedures were distinguished between breast conservative surgeries and mastectomy. Breast conservative surgeries included all the surgical procedures with a partial gland tissue removal while mastectomy comprised of the complete removal of the gland, with or without the sparing of the skin or the nipple areola complex. The axillary surgical procedures or the eventual axillary surgery omission were evaluated in the study. Resection of sentinel lymph nodes or complementary lymph nodes were considered as sentinel lymph node biopsy (SNLB); otherwise, cases with dissection of more than five nodes were classified as an axillary lymph node dissection (ALND). Operating room occupancy was considered from the entrance to the exit of the operating room and reported in minutes. Length of hospitalization was obtained from clinical notes and reported in days. Tumor staging according to the TNM classification (NCCN Guidelines) and breast cancer prognostic and predictive factors were reported after being collected from pathological reports. Five years survival and recurrence free survival were obtained from clinical note and oncological follow-up visits.

Statistical analysis

All data were submitted into the EXCEL database (Microsoft, Washington, DC, USA).

According to type anesthesia, continuous variables were compared between the Awake group and the No-Awake group using T test, and the data were reported as medians and ranges. Otherwise, Fisher's exact test was applied in cases of dichotomous variables while Monte Carlo test was used in cases of non-dichotomous variables, reported as absolute numbers and percentages. p-value <0.05 was considered to be statistically significant. For survival and recurrence free survival, Kaplan-Meier curve was used, and the significance was evaluated with Log-Rank value. All the statistical analysis was performed in SPSS statistical package version 23.0 (SPSS Inc., Armonk, NY, USA).

RESULTS

Between January 2017 and December 2018, 34 elderly patients with an ASA score ≥3 underwent breast surgery for a malignant disease. Median age was 78 years [75;95] and median of CCI was 10 [9;13]. Median follow-up was 5.43 years [2.9;6.4]. Out of 34 patients, 19 (55.9%) underwent a conservative breast surgery and 15 (44.1%) were subjected to mastectomies. No cases of tissue expander or definitive prothesis implant were performed. In 20 cases (58.9%), axillary surgery was omitted, SLNB was performed in 8 patients (23.5%), and ANLD was performed in 6 cases (17.6%). Median operative room occupancy was 74 minutes [35;142]. Post-surgical complications within thirty days were reported in 11 patients (32.4%), and no cases of reoperation were reported. 7 patients (20.6%) experienced post-operative delirium resolved within 7 days. Median hospitalization was 1 day [0;4]. Upfront non-surgical treatment was carried out in 11 patients (32.4%) in order to avoid or postpone breast surgery: 9 (26.5%) breast radiation therapy and 7 (20.6%) hormone therapy. Tumor staging according to the TNM classification and breast cancer prognostic and predictive factors are resumed in table 1 (Table 1).

Table 1. Overall tumor staging according to TNM classification and breast cancer prognostic and predictive factors.

	Overall population (n=34)
T	
T1	12 (35.3%)
T2	10 (29.4%)
T3	2 (5.9%)
T4	10 (29.4%)
N	
Nx	20 (58.8%)
N0	8 (23.5%)
N1	2 (5.9%)
N2	4 (11.8%)
Estrogen Receptor %	90 [85;95]
Progesterone %	70 [0;90]
Ki67 Index %	10 [2;40]
HER2 positivity	19 (55.9%)

Values are presented as absolute numbers and percentages for dichotomous variables and with medians and ranges for continuous variables.

Five-years overall survival was 94.5% (Figure 1a): 2 patients (5.9%) died for non-cancer related disease. Five-years overall recurrence free survival was 85.3% (Figure 1b). 16 patients (45.7%) underwent awake breast surgery while the remaining 18 patients (54.3%) underwent breast surgery under general anesthesia and were thus considered as No-Awake group. Median age of patients subjected to awake breast surgery was 86 years [75;95] *vs.* 77.5 years [76;91] in the control group; *p* value was 0.245. Median BMI was comparable between groups: 27 [23;33] *vs.* 26 [23;31], *p=0.569.* Differently, CCI was significantly higher in the Awake group with a median score of 12 [9;13] *vs.* 10 [9;11] in the No-Awake group: relative *p* value was <0.001. Median follow-up was comparable between groups: 5.5 years [3.2;6.3] in the Awake group *vs.* 5.4 years [2.9;6.3], *p*=0.334. No statistically significant difference was reported regarding the performed surgical procedure with 8 cases (50%) of breast conservative surgery performed in the Awake group *vs.* 11 (61.1%) in the control group; *p=0.515*. Axillary surgery was omitted in 10 (62.5%) cases in the Awake group and in 10 cases (55.6%) in the No-Awake population; cases subjected to SNLB and ALND were, respectively, 2 (12.5%) and 4 (25%) in the Awake group *vs.* 6 (33.3%) and 2 (11.1%), with a *p* value of 0.351.

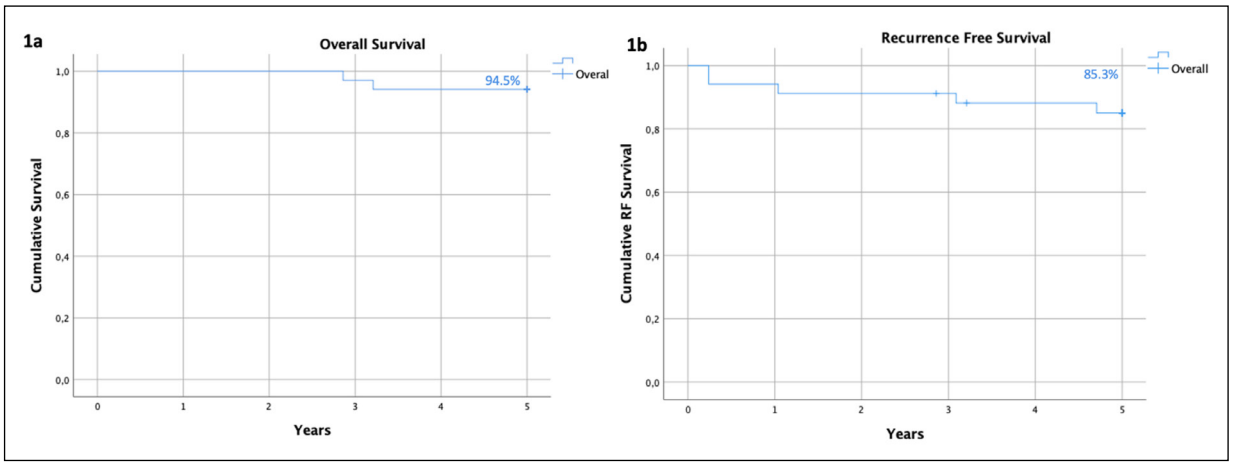

Figure 1. Five-years overall survival and recurrence free survival. **a**) Five-years overall survival; **b**) Five years recurrence free survival.

Median operative room occupancy was 57.5 minutes [35;110] in the Awake group; significantly shorter than in the group subjected to general anesthesia (82.5 minutes [35;142]), relative *p*-value was 0.050. Incidence of post-operative surgical complication was comparable between the two groups: *p*=0.152; no major complications were reported in either group, and no second surgeries were required. Differently, a significantly higher incidence of post-operative delirium was observed in patients subjected to breast surgery under general anesthesia: 6 (33.3%) *vs.* 1 case (6.3%) in the Awake group, *p*=0.050.

Median hospitalization time was 1 day [0;4] in the Awake group and 1 day [0;2] in the control group showing a statistical significant difference, *p*=0.039. In the Awake group, upfront non-surgical treatment was performed in 5 patients (31.3%) in order to avoid or postpone breast surgery *vs.* in 6 cases (33.3%) among those subjected to general anesthesia, relative *p*-value was 0.897.

5 patients (31.3%) were subjected to upfront breast radiation therapy before surgery in the Awake group *vs.* 4 (22.2%) in the control group, *p*=0.703. 5 cases (31.3%) were treated with upfront hormone therapy prior to surgery in the Awake group *vs.* 2 (11.1%) in the control group, *p*=0.214. Tumor staging according to TNM classification and breast cancer prognostic and predictive factors between the two groups are resumed in Table 2.

Five-years overall survival was comparable between the groups as shown in Figure 2a; 93.8% in the Awake group *vs.* 94.4% in patients subjected to general anesthesia, relative log rank was 0.950 (Figure 2a). No cases of cancer related death were reported in either group. Five-years recurrence free survival was 93.8% in the Awake group *vs.* 77.9% in cases subjected to general anesthesia, *p*=0.184.

DISCUSSION

Increasing life expectancy, reported in the last decades in European and North American countries, has been associated with an increase in chronic and oncological disease[1,16]. Accordingly, breast cancer in elderly patients has become more frequent and nowadays represents more than 30% of new diagnoses[2]. Breast cancer in elderly women presents apparently with favorable prognostic factors, yet is also associated with higher comorbidity and elevated anesthesiologic risk, which leads physicians to provide less than the standard breast cancer care[9,17]. Axillary surgery, adjuvant radiation therapy and/or chemotherapy are frequently omitted in high-risk patients due to the potential associated morbidity, and surgery is substituted with endocrine therapy or radiotherapy [10,18]. Despite the potential benefits of surgical omission in terms of related morbidity, this strategy seems to be associated with an improvement of the oncological outcomes[12,13,19,20]. Moreover, in cases of tumor progression after primary endocrine therapy or radiotherapy, cancer complications (e.g., ulcerated lesion, cancer hemorrhage) could be observed, leading to a delay in the required breast surgery and potentially resulting in less conservative approaches[21,22]. In our study, roughly 30% of patients received primary treatments with endocrine therapy or radiotherapy, as they were not considered suitable for surgery at the time of diagnosis. Due to cancer progression and its associated morbidity, these patients were subsequently subjected to breast surgery without severe complications. In our opinion, considering the continuous increase in life expectancy

Table 2. Overall tumor staging according to TNM classification and breast cancer prognostic and predictive factors in the Awake and control group.

	Awake group (n=16)	No-awake group (n=18)	*p*-value
T			0.606
T1	5 (31.3%)	7 (38.9%)	
T2	4 (25%)	6 (33.3%)	
T3	2 (12.5%)	0	
T4	5 (31.3%)	5 (27.8%)	
N			0.341
Nx	10 (62.5%)	10 (55.6%)	
N0	2 (12.5%)	6 (33.3%)	
N1	2 (12.5%)	0	
N2	2 (12.5%)	2 (11.1%)	
Estrogen Receptor %	90 [90;95]	92.5 [85;95]	0.133
Progesterone %	70 [0;90]	65 [5;90]	0.01
Ki67 Index %	10 [5;30]	15 [2;40]	0.194
HER2 positivity	11 (68.7%)	8 (44.4%)	0.185

Values are presented as absolute numbers and percentages for dichotomous variables and with medians and ranges for continuous variables.

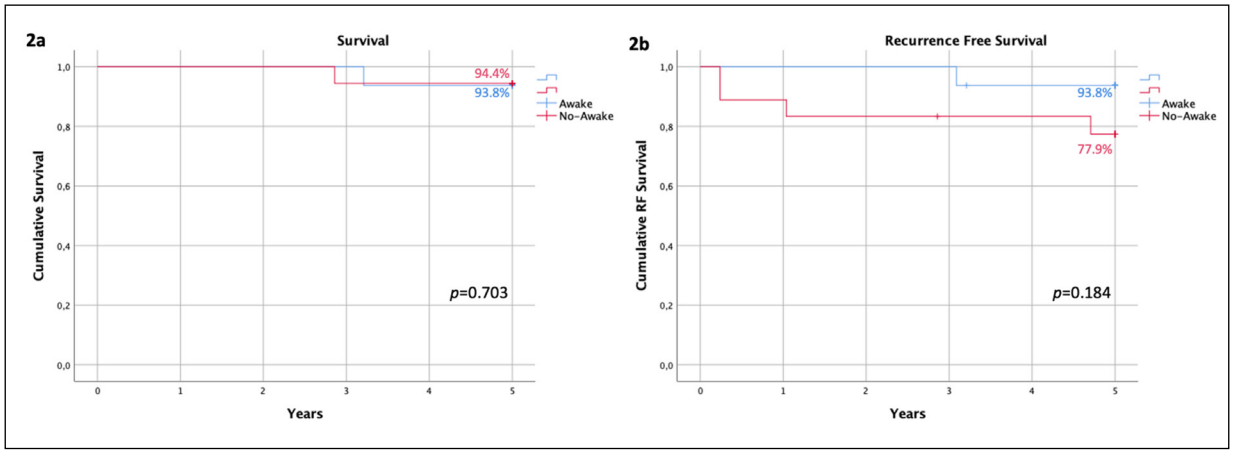

Figure 2. Five years survival and recurrence free survival in the Awake and control groups. **a**) Five-years overall survival between Awake and No-Awake groups; **b**) Five-years recurrence free survival between Awake and No-Awake groups. Log Rank is reported as *p*.

and the consequential rise of breast cancer incidence in advanced-aged patients, specific guidelines for cancer management in elderly women are required.

Awake surgery is a strategy aimed at reducing potential anesthesiologic risks, especially in frail patients[23]. Its potential advantages have been demonstrated in different types of surgery and reported in numerous studies[24-26]. This strategy was adopted during the COVID-19 emergency in order to reduce operatory room occupancy and minimize delays in cancer treatments[14,15]. Furthermore, by reducing surgical time, the awake strategy allows for a reduction in healthcare costs[27]. We strongly believe that awake breast surgery indeed reduces surgical time, as reported in our analysis.

In recent times, due to the favorable prognostic factors in elderly patients with breast cancer and despite the lack of clear guidelines, a de-escalation in breast cancer treatments has been implemented[28,29].

In our study, we observed many cases in which axillary surgery was omitted, falling in line with these trends. The omission of axillary surgery in elderly patients, especially in those with cN0, could represent a reasonable approach[30-32]. In fact, even in cases of lymph node metastases in elderly breast cancer patients, adjuvant chemotherapy is often avoided on account of the multiple and various comorbidities. Therefore, surgical axillary staging would not provide additional information. Moreover, it would prolong the surgical times and increase the associated risks and costs[30]. The anesthesiological regimen used in our study does not impact the choice of surgical procedure or the decision to omit a certain treatment option; rather, the decision for surgical de-escalation is strongly correlated to the patients' comorbidity and frailty.

In our analysis, patients subjected to general anesthesia presented more frequently with episodes of post operative delirium. This complication is a common and serious postoperative disease, strongly correlated with anesthesiologic and pain medications as opioids[33,34]. We strongly believe that awake surgery with simultaneous locoregional anesthesia could reduce the occurrence of post-operative delirium[35]. Length of hospitalization was reduced in patients subjected to awake breast surgery. In a previous study which analyzed all breast cancer patients, we did not report this difference[14]. Probably, this difference was correlated with the post operative delirium reported in elderly patients which significantly influences the length of hospitalization[35].We believe that awake surgery allows for a quicker recovery after surgery with a potential reduction of delirium complication and a potential positive impact on the oncological outcome[36-38].

The lesser impairment of the immune system associated with awake surgery strategies was reported in the literature, but its oncological advantages are still debated[24-26]. While a reduction of disease recurrence was observed in the Awake group, due to the absence of a statistically significant difference and the small sample analyzed, we are not able to fully assess the oncological advantages of this strategy. In order to clarify and highlight its potential, further prospective and molecular studies are needed to evaluate this important issue. Other limitations of the study include its retrospective design and the fact that patients subjected to awake breast surgery presented with higher comorbidity. Additional randomized clinical trials are required in order to confirm the advantages of this less invasive strategy in terms of recovery following breast surgery.

CONCLUSIONS

Awake breast surgery in elderly patients, especially in frail and highly comorbid ones, could reduce the incidence of postoperative delirium by enabling a shorter hospitalization and allowing for a faster recovery following surgery while reducing healthcare costs. Additionally, reducing OR occupancy could improve availability of resources.

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The data are available. Requests for material must be addressed to the corresponding authors with valid motivation and declaration of purpose of use.

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