The Validation Study of Adjuvant Online Using Iranian Breast Cancer Data

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Abstract

Introduction: Adjuvant Online! (AOL) is used extensively by oncologists in Iran to treat patients with breast cancer; however, it has never been validated for use in Iran, and its predictions might not be applicable to Iranian patients. The aim of this study was to evaluate the usefulness of this program in predicting the outcomes of Iranian patients with breast cancer.

Patients and methods: 368 patients who were treated between 1997 and 2010 at Jorjani Cancer Center entered the study. Data for each patient, including tumor size, number of positive nodes, tumor grade, ER status, and adjuvant systemic therapy, were entered into the AOL program (version 8.0), and the calculated disease free survival (DFS) was compared with the observed one. Analyses were performed using Cox regression modeling and SPSS 17.0 software, and P values < 0.05 were considered significant.

Results: Observed disease free survival (DFS)in our study was 72 months, while the calculated DFS by AOL was 68 months. In all subgroups of AOL, calculated DFS was less than observed DFS except for patients receiving Tamoxifen + Aromatase Inhibitors + Ovarian Ablation hormone therapy, for whom the calculated DFS was 2 percent more than the observed one.

Conclusion: AOL underestimated overall survival and disease free survival rates in Iranian patients with breast cancer, which in our opinion was mainly due to the shorter period of follow-up in our study. Although AOL is widely used by Iranian oncologists, we believe that developing an Iranian version of a prediction tool would better predict the prognosis of our patients.

Key words: Breast cancer, Adjuvant Online!, Iranian patients.

Introduction

Cancer is the third most common cause of mortality in Iran, following cardiovascular disorders and road traffic accidents. Breast cancer is one of the most common malignancies among women worldwide, and it is the most common malignancy among Iranian women [1].

Improvements in the efficacy of adjuvant chemotherapy have improved the prognosis of early breast cancer [2,3]. It is now acknowledged that while adjuvant drug therapy can improve survival in breast cancer patients, the decision to prescribe it for early breast cancer patients is complex, as inaccurate outcome predictions can result in over or under treatment of patients [2,3]. Estimating the patients' survival and knowing the likely benefits and side effects of adjuvant therapy are key factors in making treatment decisions following surgery for invasive, early-stage breast cancer [3,4].

The choice of breast cancer treatments isbased mainly on international guideline recommendations such as ESMO (European Society for Medical Oncology), NCCN (National Comprehensive Cancer Network), St. Gallen consensus, etc. These evidence-based guidelines give recommendations based on stage of disease, pathologic characteristics of the tumor, and the reported efficacy of treatment [2]. Recently, several predictive models or programs have been developed to predict outcomes for early breast cancer patients, including the Nottingham Prognostic Index (NPI), Adjuvant! and Predict [2,4,6,8]. One widely used program is Adjuvant! Online (AOL), a web-based, open-access computer

program that estimates the prognosis and potential benefit of a particular treatment in cancer patients. For breast cancer, it predicts patient outcomes at 10 years [4,9].The mortality estimates used in AOL are based on 10-year observed overall survival (OS) of over 30000 women aged 36-69, who were diagnosed between 1988-1992 and recorded in the Surveillance, Epidemiology and End Results (SEER) registry in the United States [4,10]. AOL requires six inputs that are well established as powerful predictors of mortality and recurrence: patient age, tumor size, grade, hormone receptor status, number of positive lymph nodes, and comorbidity level [3]. By means of these prognostic criteria, AOL is able to predict the 10-year overall survival, breast cancer-specific survival, and event (recurrence)-free survival, for each unique array of prognostic factor data entered. In addition, AOL calculates the absolute survival benefit of any proposed adjuvant therapy by using treatment effect estimates from meta analyses and randomized controlled trials, to adjust its mortality and recurrence rates proportionately [5,10]. This program is widely used worldwide [2,5,7], and has been externally validated in Western patients with breast cancer. It has shown acceptable prediction for survival of patients, however, because the majority of the population under the study of AOL are Caucasian, its results might not be applicable to other nations. In a Canadian study on 4083 patients, there was no significant difference between observed and calculated (by AOL) overall and event-free survival [2]. However, a study on 1065 patients with early stage breast cancer in UK showed that AOL predictions were, on the whole, overoptimistic, and clinicians must use this program with care. The authors mention higher post-recurrence mortality of breast cancer patients in UK compared to US as one of the main reasons for this difference [5]. Furthermore, in an Asian study on 631 Malaysian patients, the predicted OS calculated by AOL was significantly higher than the observed OS (70.3% vs 63.6%). The authors have concluded that AOL is capable of discriminating between good and poor survivors after breast cancer in Asian women, however, the model is overoptimistic, and should be validated, using a large multicenter cohort of Asian breast cancer patients, to improve its utility in Asian settings [8]. Similarly, although oncologists in Iran use Adjuvant! Extensively, it has never been validated for use in Iran, thus its predictions might not be applicable to Iranian patients. Therefore, in this study we aimed to evaluate the usefulness of this program in predicting the outcomes of Iranian patients with breast cancer.

Patients and methods

The clinical data were extracted from medical records of the Jorjani Cancer Center. Among 3653 female patients with breast cancer who were treated at this center between 1997 and 2010, after applying the exclusion criteria, 368 entered the study. The exclusion criteria were as follows: incomplete local or systemic treatment; metastatic disease; presence of macroscopic or microscopic positive surgical margins; patients with skin or chest wall involvement at presentation; inflammatory breast cancer; bilateral disease; receipt of neoadjuvant chemotherapy; previous history of chemotherapy for any reason; previous history of breast cancer; patients with any missing data regarding the studied variables (except from mortality); and patients with less than 24 months of follow up. Data for each patient, including tumor size, number of positive nodes, tumor grade, ER status and adjuvant systemic therapy, were entered into the AOL program (version 8.0). Chemotherapy regimens were divided into three generations: generation one (CMF-based or less than 4 cycles of anthracycline-based), generation two (more than 4 cycles of anthracycline-based or paclitaxel-containing regimens every three weeks), and generation three (paclitaxel-containing regimens every two weeks or regimens containing docetaxel). Hormone therapy regimens were divided into five groups: group one (tamoxifen), group two (Aromatase Inhibitor, AI), group three (tamoxifen+ AI), group four (Ovarian Ablation, OA), and group five (OA+ tamoxifen or AI). For “comorbidity”, the majority of patients were categorized as having“ minor problems”. Then, predicted disease free survival (DFS) was calculated and compared with the observed data. Because information regarding mortality was not available for some patients (e.g., out of hospital deaths), overall survival was omitted from the study. Analyses were performed using Cox regression modeling and SPSS 17.0 software, and P values < 0.05 were considered significant.

Results

Mean age of the patients was 47.23 years (CI=46.17-48.28). Mean size of the tumors was 3.32cm (CI=3.14-3.5). Mean number of studied lymph nodes was 10.92 (CI= 10.31-11.54) and mean number of metastatic lymph nodes was 3.33 (CI=2.68-3.8). Seventy percent of the patients had positive estrogen receptors (ER). Observed disease free survival (DFS) in our study was 72 months, while the calculated DFS by AOL was 68 months. The difference between these two numbers is

Table 1: Results of the study in main subgroups

	Number	%	Mean % of 5-years DFS		
			AOL Pred (95% CI)	Obs (95% CI)	(Pred-Obs)
All patients	368	100	68	72	-4
Age					
< 50	244	66	70	72	-2
50-59	73	20	64	71	-5
60-69	43	12	58	63	-5
≥ 70	8	2	73	74	-1
T Stage					
0.1-1	23	7	81	85	-4
1.1-2	69	20	78	83	-5
2.1-3	103	31	66	75	-9
3.1-5	96	28	64	71	-7
>5	47	14	55.5	74	-18.5
Number of positive nodes					
0	134	36	80	87	-7
1-3	117	32	68	76	-8
4-9	85	23	55	67	-12
≥ 10	32	9	45	69	-24
Histologic grade					
Undefined	152	41	65	75	-10
1	27	7	82	84	-2
2	123	34	71	79	-8
3	66	18	61	73	-12
ER Status					
Positive	240	68	70	78	-8
Negative	113	32	63	71	-8
Chemotherapy Protocol					
No	18	5	75	-	-
Generation 1	126	34	63	71	-8
Generation 2	159	43	69	77	-8
Generation 3	65	18	71	79	-8
Hormone therapy Protocol					
NO	102	28	62	75	-13
G1: Tam	218	59	69	76	-7
G2: AI	19	5	79	-	-
G3:Tam+AI	9	2	76	81	-5
G4: OA	7	2	59	76	-17
G5: OA+Tam or AI	13	4	66	64	+2

AOL: Adjuvant Online; CI: Confidential Interval; Pred: predicted; Obs: observed ; DFS: Disease Free Survival

shown as -4 in the table, which means that the AOL estimated DFS was 4 months less than the observed DFS. The majority of recurrences (75%) occurred within 5 years of the initial diagnosis, and 7% occurred after 10 years. These findings were then calculated separately based on main AOL parameters, and calculated figures were compared with observed figures (table 1).

In all subgroups of AOL, calculated DFS was less than observed DFS, except for Tam+AI+OA hormone therapy, in which the calculated DFS was 2 percent more than the observed one. For all sizes of tumors combined, the calculated observed DFSs were quite close (less than 4 percent difference), however, by looking at increasing sizes of the tumors, this difference changed significantly to where the observed DFS was 18.5 percent more than the calculated one. Similar results were found for number of metastatic lymph nodes. In patients with N0 metastatic lymph nodes, the difference between observed and calculated DFS was 7 percent (in favor of observed); however, in patients with more than nine metastatic lymph nodes, observed DFS was 24 percent more than calculated DFS. Regarding the grade, patients with grade 1 tumor had an observed DFS closest to the calculated one; however, this difference was significant for grades 2 and 3, as well as for undefined grades (12 months for grade 3 tumors). No difference was found between observed and calculated DFSs based on hormone receptor status or the prescribed chemotherapy regimens.

We also assessed our results based on some prognostic factors that are not included in AOL, such as lymphovascular and perineural invasion (table 2).

By considering the total number of evaluated lymph nodes (both normal and metastatic), the least difference between observed and calculated DFS was seen in patients in whom 4-10 lymph nodes were evaluated. In case of a recurrence, regardless of the time between diagnosis and relapse, the calculated DFS was more than the observed one for all patients, and the least difference was seen for patients in whom the cancer recurred between 3-5 years after diagnosis.

Discussion

To our knowledge, this is the first paper to study the validity of the AOL tool in an Iranian population. Studies on the accuracy and validation of AOL in different countries and ethnic groups have achieved different results. Results of a study on 456 women from a French data set, and 295 women from a

Table 2: Results of the study in subgroups not included in AOL

	Number	%	Mean % of 5-years DFS		
			AOL Pred (95% CI)	Obs (95% CI)	(Pred-Obs)
All patients	368	100	66.14 (64.29-67.99)	74.20 (72.19-76.20)	-8.06
LVI					
Negative	84	42	74	83	-9
Positive	115	58	68	77	-9
PNI					
Negative	71	45	74	82	-8
Positive	87	55	68	76	-8
Number of examined nodes					
1-3	25	7	76	86	-10
4-9	168	46.5	68	73	-5
≥ 10	168	46.5	66	78	-12

AOL: Adjuvant Online; CI: Confidential Interval; Pred: predicted; Obs: observed ; DFS: Disease Free Survival

Dutch data set, demonstrated that AOL prediction was well calibrated overall for the French data set, but failed in some subgroups of high-grade and HER2 positive patients. In the Dutch data set, the overall 10-year survival was over estimated by AOL, particularly in patients less than 40 years old. The authors concluded that AOL needs updating to adjust overoptimistic results in young and high-grade patients, and should consider new predictors such as Ki67, HER2 and Mitotic Index [7]. Another study on 559 Taiwanese breast cancer patients concluded that AOL accurately predicted 10-year outcomes in low-risk breast cancer patients, although the results were less accurate in the high-risk subgroup, where AOL overestimated breast cancer-specific survival [11]. A Canadian study on 4,083 women with T1-2, N0-1, M0 breast cancer found AOL a reliable tool to predict the outcome. In this study, AOL overestimated overall survival, and breast cancer specific survival, in women younger than age 35 years or with lymphatic or vascular invasion (LVI). The authors concluded that patients younger than age 35, or with known additional adverse prognostic factors such as LVI, require adjustment of risks to derive reliable predictions of prognosis without adjuvant systemic therapy and its absolute benefits [2]. A Brazilian study on 214 patients concluded that the OS and DFS rates in their sample displayed general agreement with the one calculated by the AOL program. It followed the same pattern, and the only group which had poor concordance status was the group of patients under the age of 40 [12]. A Dutch study on 5380 patients with median follow-up of 11.7 years concluded that AOL was able to predict accurately 10-year outcomes and was of use for adjuvant treatment decision-making [13]. A Korean study on 699 patients did not find AOL to be suitable for Korean patients with breast cancer. In their study, AOL significantly overestimated overall survival, breast cancer-specific survival (BCSS), and event-free survival (EFS); therefore, the authors developed a Korean version of AOL based on AOL's parameters [14]. A study based on University Malaya Hospital-Based Breast Cancer Registry found that AOL was capable of discriminating between good and poor survivors, but overestimated the survival in Asian patients [8]. As can be seen, in the majority of studies AOL overestimated the OS or DFS, and was considered over optimistic by many authors. However, AOL predictions turned out to be pessimistic in our study. The effect of age on our results is complex. Mean age of our patients was 47.23 year, which was less than the average age in many other studies [2,4,7,11]. Younger patients tend to have fewer comorbidities and hence, better treatment tolerance. On the other hand, breast cancer is known to be more aggressive in younger individuals. Therefore, the exact effect of age on observed survival of our patients compared to predict survival remains elusive. Apart from age and ethnic (and hence, genetic) differences, we believe that the main reason for such a result is shorter duration of follow up in our patients. Mean duration of follow up was 58 (25-224) months in our study, which is shorter than that of patients in AOL database. In spite of this major bias, it is important to mention that the majority of the relapse and death events usually occur during the first three years, tending to stabilize at the 3 to 10 years follow-up interval [12,15]. Therefore, we think that by continuing the follow-up of these patients until we are able to reach a median of ten years, our results will have more concordance with that of AOL.

Conclusion

AOL underestimated OS and DFS rates in Iranian patients with breast cancer, which in our opinion was mainly due to a shorter period of follow-up in our study. Although AOL is widely used by Iranian oncologists, we believe that developing an Iranian version of a prediction tool would better predict the prognosis of our patients.

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