

Research Article

Open Access, Volume 5

Androgen Receptor as a Prognostic and Predictive Factor for Response to Aromatase Inhibitors Among Female Patients with Invasive Luminal A Breast Cancer

Manar Montasser Mohamed^{1*}; Muhammad Solaiman Muhammad²; Ahmed Mostafa Elzawawy²; Wael Abdou Hassan³; Soheir Elsayed Abd Elmohsen²; Marwa A. Suliman²

¹Department of Oncology, Suez Canal Authority Hospitals, Ismailia, Egypt.

²Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.

³Department of Pathology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.

Abstract

Introduction: Estrogen receptor score of expression is an important predictive and prognostic marker in luminal A invasive breast cancer. Androgen receptor in breast cancer was studied and showed different prognostic data among the different populations.

Methods: Retrospective-prospective cohort (historical cohort) study of 43 files of female patients with Hormonal Receptor positive (HR+ve) invasive breast cancer patients; classified/stratified and tested for Androgen Receptor score of expression, considering Time to Tumor Progression (TTP) as primary end point, and Overall Survival (OS) as second end points.

Results: with a mean follow-up period of 66 months (about 5.5 years), AR (score5) had the best prognosis in luminal A (50% had TTP to the 7th year and 50% had OS to the 9th year).

Conclusion: AR (score 5) had the best prognosis in luminal A invasive breast cancer female patients; for both TTP and OS.

Keywords: Overall survival (OS); Time to tumor progression (TTP); Androgen receptor (AR).

Introduction and rationale

Androgen Receptor (AR) expression was found to be related to a favorable prognosis in Breast Cancers (BC) expressing estrogen receptor. AR seems to inhibit the cellular proliferation induced by estradiol and to have a favorable prognostic value. AR might modulate the ER signaling by interfering with both genomic and non-genomic actions [5].

In vitro, in estrogen receptor – positive (ER-positive) ZR75 and MCF-7 cells, activated AR up-regulates the estrogen receptor – β (ER β) promoter and lastly inhibits cancer cell growth, as ER β prevalently acts as a tumor suppressor in BC [15].

In several specimens of Tamoxifen-resistant BC, low ER mRNA and high AR mRNA levels were detected. Treatment with the anti-androgen Bicalutamide reversed this resistance and indicated that AR signaling is directly involved [2]. AR was found to be also

Manuscript Information: Received: Oct 07, 2025; Accepted: Nov 04, 2025; Published: Nov 11, 2025

Correspondance: Manar Montasser Mohamed, Department of Oncology, Suez Canal Authority Hospitals, Ismailia, Egypt.

Email: manarmontasser@med.suez.edu.eg

Citation: Mohamed MM, Muhammad MS, Elzawawy AM, Hassan WA, Elmohsen SEA, et al. Androgen Receptor as a Prognostic and Predictive Factor for Response to Aromatase Inhibitors Among Female Patients with Invasive Luminal A Breast Cancer. J Oncology. 2025; 5(2): 1188.

Copyright: © Mohamed MM 2025. Content published in the journal follows creative common attribution license.

responsible for the Aromatase Inhibitor (AI) resistance in ER-positive BC cells [14].

This study was done to evaluate the expression of Androgen receptor and to correlate its degree of expression with the different clinicopathological features for breast cancer patients; to be able to bring new option of treatment and new hope and of course; for better lifestyle for breast cancer patients attending Clinical Oncology and Nuclear Medicine department at Suez Canal University Hospital.

Subjects & methods

It was a Retrospective-Prospective Cohort Study (to study the correlation between score/degree of androgen receptor expression and the clinicopathological features and prognosis for simple random sample from all triple negative invasive breast cancer patient attending clinical oncology and nuclear medicine department in Suez Canal university hospital in period from January 2015 until December 2019).

Patients with unknown hormonal receptors status and patients who refuse to participate in the study were excluded.

When diagnosed as breast cancer patient, the patient is referred to our clinical oncology and nuclear medicine department to start the plan of management. Routinely, the paraffin block is requested to test for hormonal receptors namely: Estrogens-Receptor, Progesterone-Receptor and HER-2neu. Then, the patient will be asked whether to accept or to refuse testing for the Androgen Receptor using his/her same initial paraffin block without any new tissue biopsy. Result of the Androgen receptor expression was correlated to the patient clinicopathological data already present in the patient archive file records in the department. Data was collected and coded then entered as a spread sheets using SPSS. Patients were categorized into groups having the same clinicopathological features and treatment received; in order to avoid confounding.

Data was analyzed using SPSS. Data are presented as tables and graphs, t test was used to compare between quantitative data expressed as mean and standard deviation. P value < 0.05 was considered as significant. Kaplan Meier curves were used to estimate survival.

Concerning ethical considerations, Data was collected from archive files in Suez Canal University hospital Clinical Oncology Department (SCUCOD). Approval of the staff responsible in the SCUCOD and approval of the Ethics committee in the Faculty of Medicine- Suez Canal University were obtained before starting field work. Confidentiality was maintained. The patient had the right to accept or to refuse participating in the study. The study had no harm on the patient; and no invasive maneuver. The patient had the right to cancel his participation in the study at any time and without giving any excuse.

Results

A mean of 162 patients per year attended clinical oncology department in Suez Canal University hospital, in the period between January 2015 and December 2017. Hence, the sample size was calculated to provide 95% confidence interval and to ensure reliability of Data. 107 female patients with breast cancer were tested

for androgen receptor on their paraffin block.

Regarding molecular classification; 43 patients were Hormonal Receptor (HR) positive, HER2Neu negative. 39 had ER, PR +VE/HER2Neu –ve; while 4 had ER +ve, PR and HER2Neu –ve. 30 patients were triple negative, 24 patients were HER2Neu positive while only 10 patients had triple positive breast cancer. Here, we study only luminal A patients.

43 patients' files were included and studied. 43 paraffin blocks – corresponding to each of the 30 patients/files were tested for androgen receptor expression via immunohistochemistry. Sections from the selected paraffin blocks were cut into 4 micrometers thick sections for Immunohistochemical (IHC) staining. Slides were prepared and incubated with primary anti-AR antibody (Lot and Company). This was followed by incubations with the appropriate secondary antibody (Lot and Company). All slides are lightly counterstained with hematoxylin for 30s prior to dehydration and mounting.

Immunohistochemical scoring Invasive tumor cells with nuclear reaction to AR antibody were considered positive. Semi-quantitative analysis of stained tissue sections was performed through modified Allred scoring system guidelines**. Positive cells were counted in 3 different high-power fields (hpf) (400x) (Figure 1) and the average number was calculated. Individual scores of the percentage of positive cells (0–5) and the staining intensity of the cytoplasm (0–3) were summed up to obtain the final grades. The percentage of positive cells was set as follows: 1- less than 10 positive cells; 2- from 10 to 20 of positive cells; 3- from 20 to 50 positive cells; 4- from 50 to 70 positive cells; and score 5- more than 70 positive cells. The staining intensity of positivity in the cytoplasm was scored as: 1-weak; 2-moderate; and 3-strong.

Final score was calculated by the sum of number of positive cells in HPF and the intensity of staining of the cytoplasm. Final score of Zero is considered negative. Final score of 3 in addition to Zero is considered low

Figure 1: Androgen receptor expression with Hematoxylin and Eosin staining Androgen receptor degree of expression was estimated by the number of positive cells per high power field plus the intensity of its staining; both yielding a final score.

Final score of androgen receptor expression in our study ranged from 0 then 3 to 8. Score was defined as follows:

1. → Negative/ No androgen receptor expression
2. → Low positive expression
3. → Low to intermediate expression
4. → Intermediate expression
5. → Intermediate to high expression
6. → High expression
7. → Highest / Very high expression

Patients' characteristics including demographic, different clinic-pathological data are summarized in the table below (Table 1).

Table 1: Luminal A patients' characteristics.

Comparison 2 luminal A		Number	Percentage	Multifocality		43	100%
Age at diagnosis		43	100%	—	No multifocality	39	90.7%
—	Younger than 35	11	25.6%	—	Multifocality	2	4.6%
—	36-50 years	23	53.5%	—	Unknown/ no surgery done	2	4.6%
—	Older than 50 years	9	20.9%	Early versus advanced		43	100%
Menopausal status at diagnosis		43	100%	—	Early	23	53.5%
—	Premenopausal	34	79.1%	—	Advanced metastatic	2	4.6%
—	Postmenopausal	9	20.9%	—	Resectable advanced	18	41.9%
Body Mass Index at diagnosis		43	100%	Neoadjuvant chemotherapy if any		43	100%
—	Obese	18	41.9%	—	No	41	95.3%
—	Overweight	14	32.6%	—	Yes	2	4.7%
—	Average	4	9.3%	Regimen of neoadjuvant chemotherapy if any		43	100%
—	Underweight	7	16.3%	—	None received	41	95.3%
Co-morbidities		43	100%	—	3 FEC then 3 Vinorelbine/Cisplatin	2	4.7%
—	No history of any chronic illness	36	83.7%	Estrogen Receptor		43	100%
—	Hypertension	5	11.6%	—	Positive	43	100%
—	Hypertension and diabetes mellitus	2	4.6%	—	Negative	0	0%
Presenting symptom		43	100%	Progesterone Receptor		43	100%
—	Breast lump	41	95.3%	—	Positive	34	79%
—	Easy fatiguability	2	4.7%	—	Negative	9	21%
Side		43	100%	Ki67%		43	100%
—	Right breast	20	46.5%	—	Higher or equal to 20%	2	4.6%
—	Left breast	23	53.5%	—	Lower than 20%	2	4.6%
Operation		43	100%	—	Unknown	39	90.7%
—	Modified Radical Mastectomy	36	83.7%	Molecular group		43	100%
—	Conservative breast surgery	5	11.6%	—	ER, PR+ve, HER2neu –ve	34	79%
—	Biospy as metastatic	2	4.7%	—	ER +VE, PR, HER2Neu -ve	9	21%
Histopathological subtype		43	100%	Adjuvant Chemotherapy		43	100%
—	Invasive ductal carcinoma	41	95.3%	—	No adjuvant chemotherapy	1	2.3%
—	Invasive lobular carcinoma	2	4.7%	—	6 FEC	32	74.4%
Grading		43	100%	—	4 AC then 12 Paclitaxel weekly	5	11.6%
—	Grade 1	5	11.6%	—	4 AC then 4 Paclitaxel every 3 weeks	3	7%
—	Grade 2	33	76.8%	—	4 FEC then 4 Paclitaxel/ Carboplatin	2	4.6%
Grade 3		5	11.6%	Post-operative Radiotherapy		43	100%
Tumor size		43	100%	—	No adjuvant radiotherapy	7	16.3%
—	T1	9	20.9%	—	50Gy/25#	34	79%
—	T2	27	62.8%	—	-45Gy/18#	2	4.6%
—	T3	5	11.6%	Hormonal Treatment and/or maintenance		43	100%
—	Locally advanced T4	2	4.7%	Capecitabine		11	25.6%
Nodal status		43	100%	—	Letrozole	7	16.3%
—	N0	16	37.2%	—	Letrozole + Capecitabine	18	41.9%
—	N1	7	16.3%	—	Tamoxifen		
—	N2	7	16.3%	Tamoxifen for 2 years then Letrozole		7	16.30%
—	N3	13	30.2%	Androgen Receptor Expression Final Score		43	100%
Distant metastasis		43	100%	0		2	4.70%
—	M0	41	95.3%	-3		9	20.90%
—	M1	2	4.7%	-5		9	20.90%
Extranodal extension		43	100%	-6		7	16.30%
—	No	25	58.1%	-7		9	20.90%
—	Positive	16	37.2%	-8		7	16.30%
—	Unknown as no surgery/ lymph node dissection done	2	4.7%				
Surgical margins		43	100%				
—	Free	41	95.3%				
—	Unknown as no surgery done	2	4.7%				
Multicentricity		43	100%				
—	No multicentricity	36	83.7%				
—	Multicentricity	5	11.6%				
—	Unknown/ no surgery done	2	4.6%				

Cross Correlation of different scores/degrees of androgen receptor expression against multiple variables are illustrated below in the following Kaplan Meier survival Curves. Scores 0 to 8 against many variables tested separately 66 Androgen Receptor Score in Breast Cancer to avoid confounding. Variables: Age, Menopausal status, body mass index, early versus advanced stage.

Time to tumor progression:

Cross Correlation of different scores/degrees of androgen receptor expression against multiple variables are illustrated below in the following Kaplan Meier survival Curves. Scores 0 to 8 against many variables tested separately 66 Androgen Receptor Score in Breast Cancer to avoid confounding. Variables: Age, Menopausal status, body mass index, early versus advanced stage.

Time to tumor progression:

Generally:

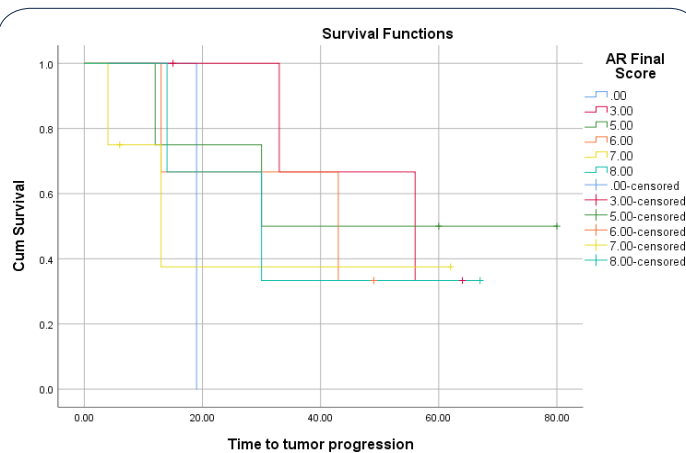


Figure 1: Time to tumor progression in luminal A patients generally.

This Kaplan-Meier curve (Figure 1) shows time to tumor progression when comparing the levels of androgen receptor expression in luminal A patients generally; as follows:

- Score 3: 100% of patients survived for → 34 months... 64% of patients survived for Regular 57 months
- Score 5: 100% of patients survived for → 13 months... 75% of patients survived for → 30 months... 50% of patients survived for → 80 months
- Score 0: 100% → 18 months.

(with overall maximal standard error: 0.750)

With body mass index:

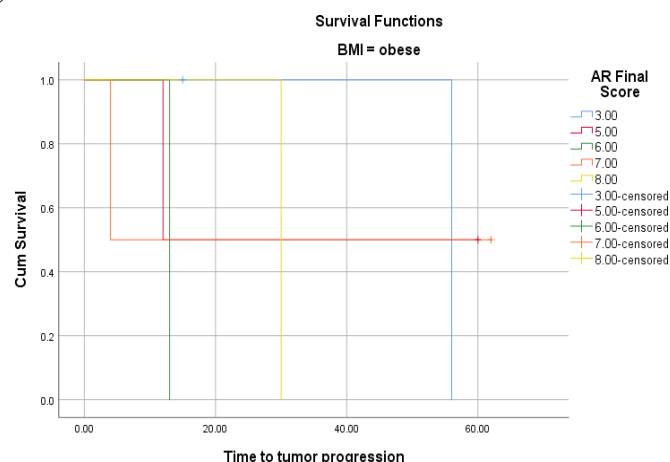


Figure 2: Time to tumor progression in luminal A obese patients.

This Kaplan-Meier curve (Figure 2) shows time to tumor progression when comparing the levels of androgen receptor expression in luminal A obese patients as calculated by body mass index (BMI); as follows:

- Score 3: 100% → 55 months
- Score 8: 100% → 30 months
- Score 5: 100% → 14 months... 50% → 60 months
- Score 7: 100% → 7 months... 50% → 63 months. (with overall maximal standard error: 0.500)

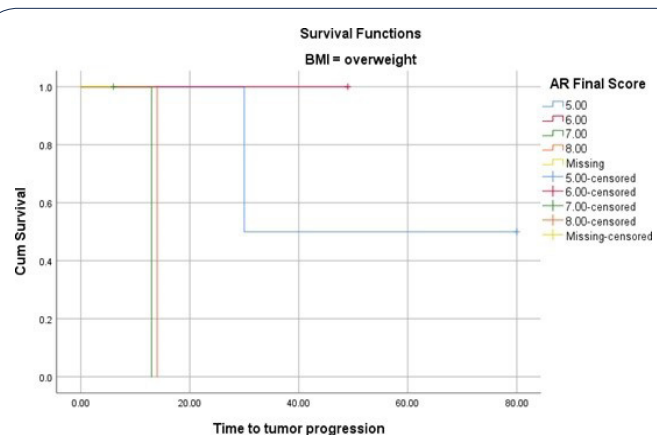


Figure 3: Time to tumor progression in luminal A overweight patients.

This Kaplan-Meier curve (Figure 3) shows time to tumor progression when comparing the levels of androgen receptor expression in luminal A overweight patients as calculated by Body Mass Index (BMI); as follows:

- Score 6: 100% → 50 months
- Score 5: 100% → 30 months... 50% → 80 months
- Score 8: 100% → 16 months
- Score 7: 100% → 15 months. (with overall maximal standard error: 0.500)

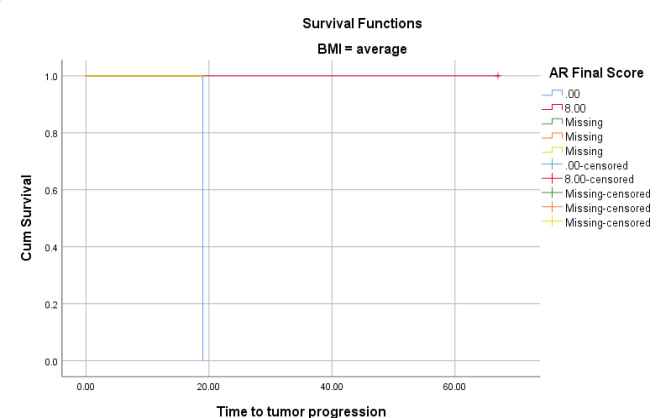


Figure 4: Time to tumor progression in luminal A average-weight patients.

This Kaplan-Meier curve (Figure 4) shows time to tumor progression when comparing the levels of androgen receptor expression in luminal A average Body Mass Index (BMI) patients; as follows:

- Score 8: 100% → 70 months
- Score 0: 100% → 18 months. (with overall maximal standard error: 0.000)

This Kaplan-Meier curve (Figure 5) shows time to tumor progression when comparing the levels of androgen receptor expression in luminal A underweight patients as calculated by body mass index (BMI); as follows:

- Score 3: 100% → 34 months... 50% → 64 months
- Score 6: 100% → 44 months. (with overall maximal standard error: 0.500)

With age group

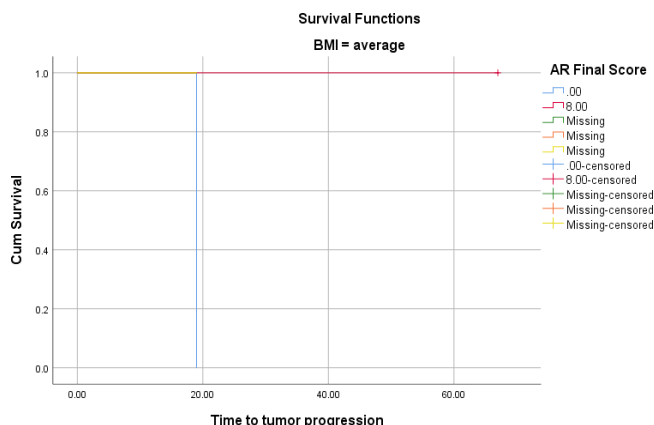


Figure 5: Time to tumor progression in luminal A underweight patients.

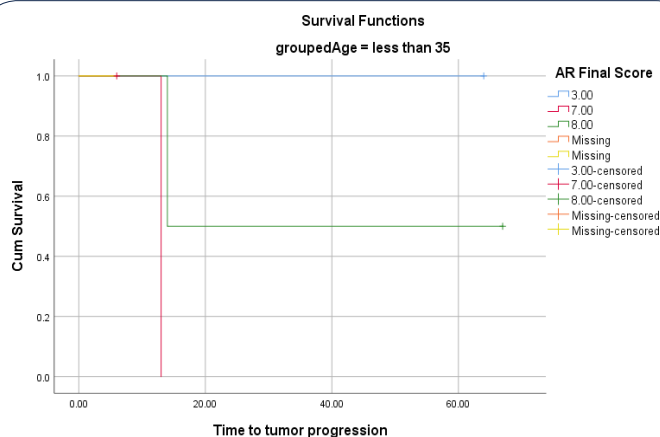


Figure 6: Time to tumor progression in luminal A patients with age less than 35 years.

This Kaplan-Meier curve (Figure 6) shows time to tumor progression when comparing the levels of androgen receptor expression in luminal A patients with regard to age less than 35 years; as follows:

- Score 3: 100% → 64 months
- Score 8: 100% → 16 months... 50% → 68 months
- Score 7: 100% → 14 months.

(with overall maximal standard error: 0.500)

This Kaplan-Meier curve (Figure 7) shows time to tumor progression when comparing the levels of androgen receptor expression in luminal A patients with regard to age 36 to 50 years; as follows:

- Score 3: 100% → 34 months... 50% → 55 months
- Score 5: 100% → 12 months... 95% → 30 months... 50% → 8 months
- Score 8: 100% → 30 months.

(with overall maximal standard error: 0.750)

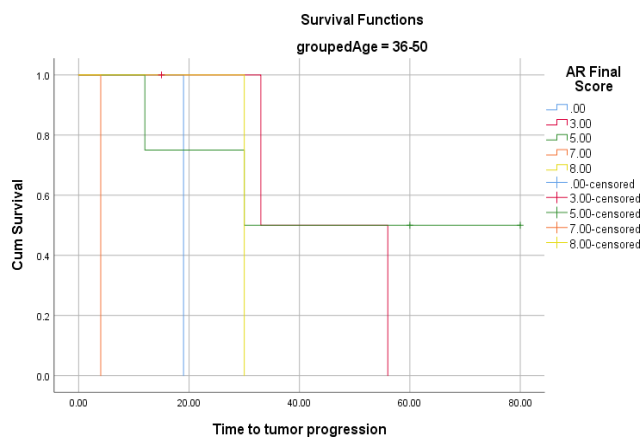


Figure 7: Time to tumor progression in luminal A patients with age 36 to 50 years.

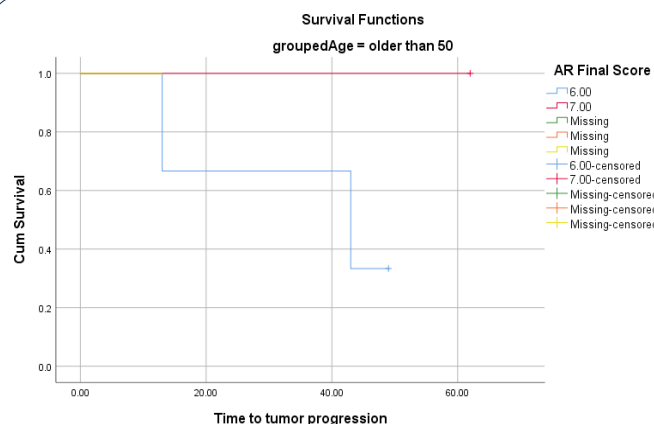


Figure 8: Time to tumor progression in luminal A patients with age older than 50 years.

This Kaplan-Meier curve (Figure 8) shows time to tumor progression when comparing the levels of androgen receptor expression in luminal A patients with regard to age older than 50 years; as follows:

- Score 7: 100% → 63 months
- Score 6: 100% → 14 months... 66% → 43 months... 33% → 50 months. (with overall maximal standard error: 0.667)

With menopausal status

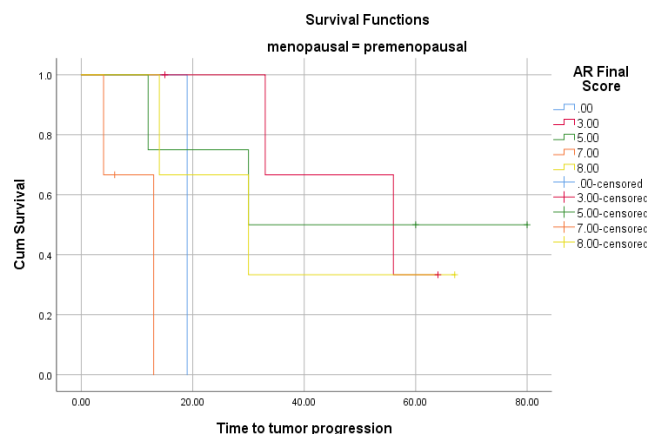


Figure 9: Time to tumor progression in luminal A premenopausal patients.

This Kaplan-Meier curve (Figure 9) shows time to tumor progression when comparing the levels of androgen receptor expression in luminal A premenopausal patients; as follows:

- Score 3: 100% → 33 months... 68% → 16 months
- Score 5: 100% → 16 months... 75% → 30 months... 50% → 80 months
- Score 0: 100% → 18 months. (with overall maximal standard error: 0.750)

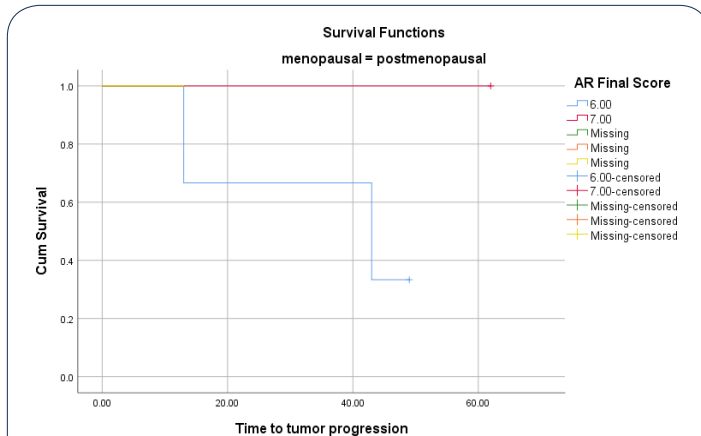


Figure 10: Time to tumor progression in luminal A postmenopausal patients.

This Kaplan-Meier curve (Figure 10) shows time to tumor progression when comparing the levels of androgen receptor expression in luminal A postmenopausal patients as follows:

- Score 7: 100% → 62 months
- Score 6: 100% → 13 months... 65% → 43 months... 35% → 48 months. (with overall maximal standard error: 0.667)

With stage early versus advanced

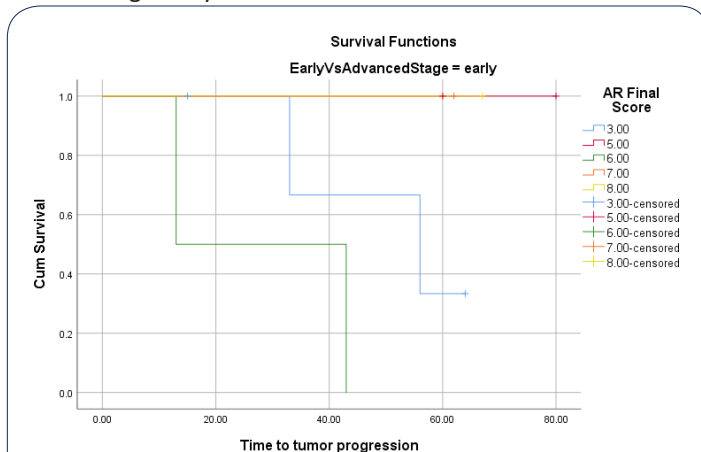


Figure 11: Time to tumor progression in luminal A patients with regard to early stage.

This Kaplan-Meier curve (Figure 11) shows time to tumor progression when comparing the levels of androgen receptor expression in luminal A patients with regard to early stage; as follows:

- Score 5: 100% → 80 months
- Score 8: 100% → 68 months
- Score 7: 100% → 62 months

- Score 3: 100% → 32 months... 64% → 55 months
- Score 6: 100% → 14 months... 50% → 44 months. (with overall maximal standard error: 0.667)

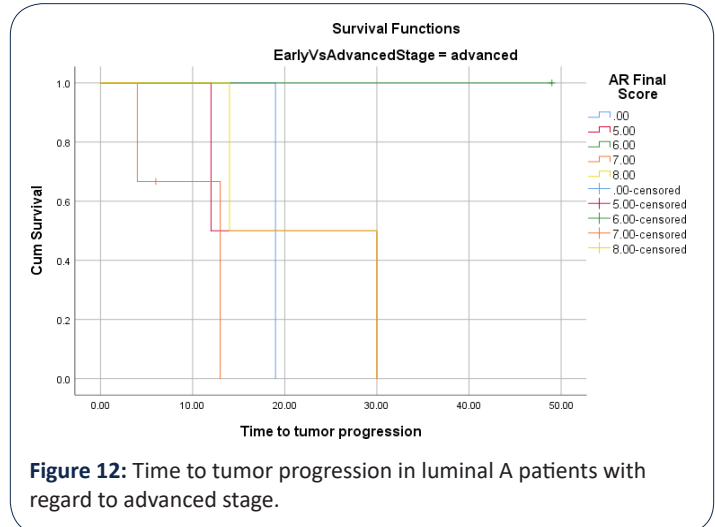


Figure 12: Time to tumor progression in luminal A patients with regard to advanced stage.

This Kaplan-Meier curve (Figure 12) shows time to tumor progression when comparing the levels of androgen receptor expression in luminal A patients with regard to advanced stage; as follows:

- Score 6: 100% → 48 months
- Score 0: 100% → 18 months
- Score 7: 100% → 7 months... 68% → 16 months... 50% → 30 months. (with overall maximal standard error: 0.667)

Response to Tamoxifen

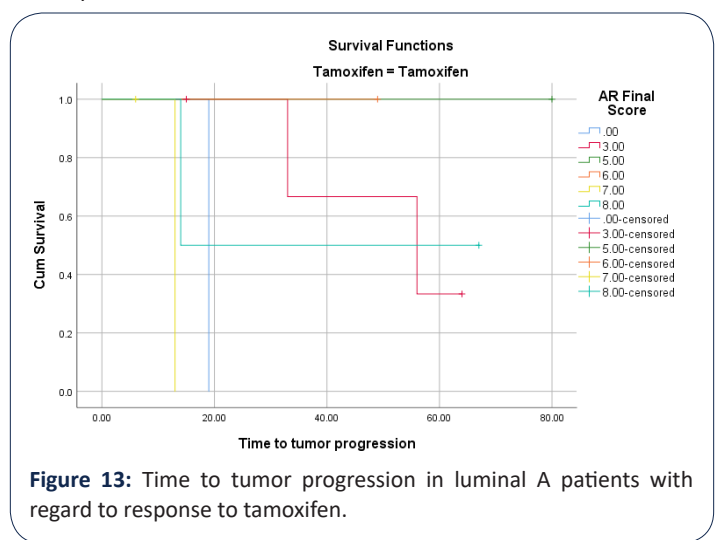


Figure 13: Time to tumor progression in luminal A patients with regard to response to tamoxifen.

This Kaplan-Meier curve (Figure 13) shows time to tumor progression when comparing the levels of androgen receptor expression in luminal A patients with regard to response to tamoxifen; as follows:

- Score 5: 100% → 80 months
- Score 3: 100% → 34 months... 65% → 55 months... 33% → 66 months
- Score 8: 100% → 15 months... 50% → 68 months
- Score 7: 100% → 14 months... (most resistant). (with overall maximal standard error: 0.667)

Response to Letrozole

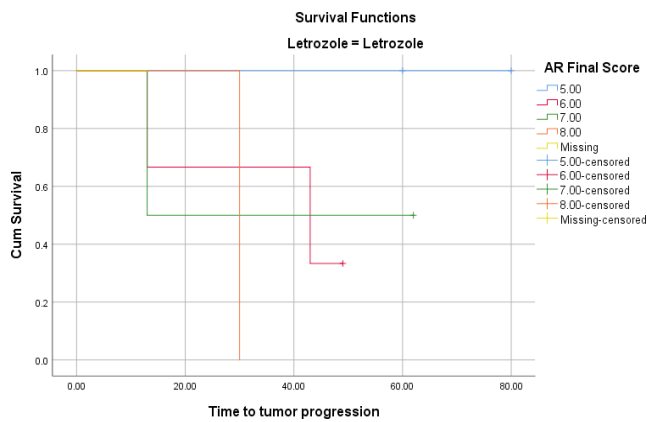


Figure 14: Time to tumor progression when comparing the levels of androgen receptor expression in luminal A patients with regard to response to letrozole.

This Kaplan-Meier curve (Figure 14) shows time to tumor progression when comparing the levels of androgen receptor expression in luminal A patients with regard to response to letrozole; as follows:

- Score 5: 100% → 80 months
- Score 7: 100% → 13 months... 50% → 64 months
- Score 8: 100% → 30 months. (with overall maximal standard error: 0.667)

Summary of TTP/PFS curves in luminal A Subgroup

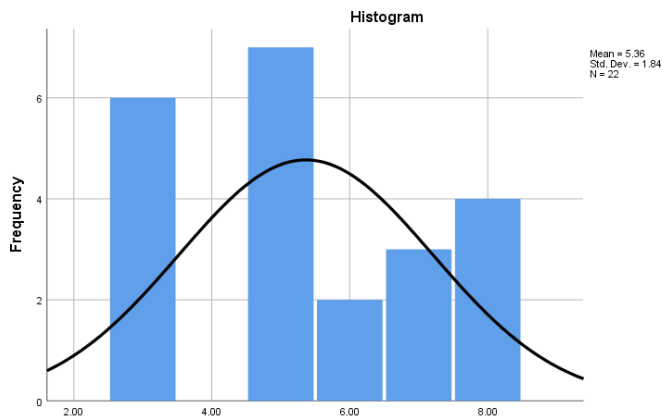


Figure 15: Score 5 as degree of androgen receptor expression is the predominant in time to tumor progression (TTP) in all luminal A patients.

This histogram (Figure 15) shows that score 5 as degree of androgen receptor expression is the predominant and has the best Time to Tumor Progression (TTP) in all luminal A patients in our study. Z score = -7.386. P-Value is < .00001. (statistically significant)

Overall survival:

Generally:

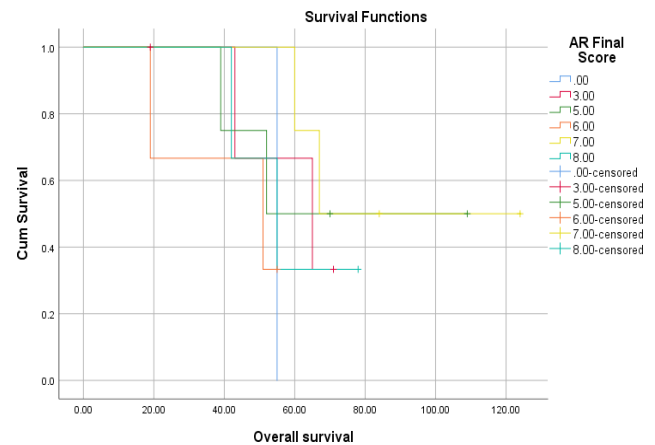


Figure 16: Overall survival in luminal A patients.

This Kaplan-Meier curve (Figure 16) shows the overall survival when comparing the levels of androgen receptor expression in luminal A patients generally; as follows:

- Score 7: 100% of patients survived for → 60 months... 78% of patients survived for → 68 months... 50% survived for → 125 months
- Score 5: 100% → 38 months... 74% → 55 months... 50% → 110 months
- Score 0: 100% → 55 months (with maximal standard error: 0.272)

With Body Mass Index:

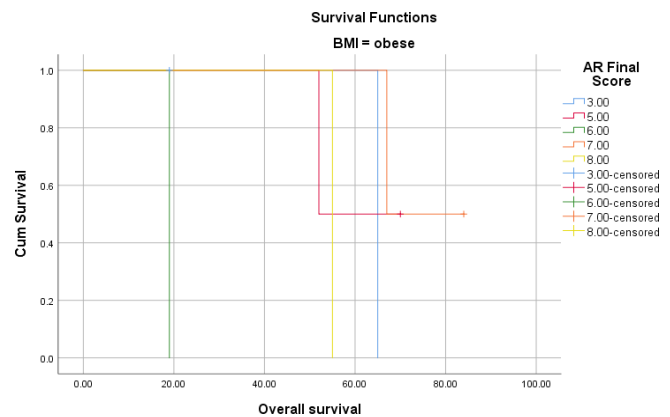


Figure 17: Overall survival in luminal A obese patients.

This Kaplan-Meier curve (Figure 17) shows the overall survival when comparing the levels of androgen receptor expression in luminal A obese patients as estimated by Body mass Index (BMI); as follows:

- Score 7: 100% → 66 months... 50% → 85 months
- Score 3: 100% → 64 months
- Score 8: 100% → 55 months
- Score 5: 100% → 50 months... 50% → 70 months (with maximal standard error: 0.354)

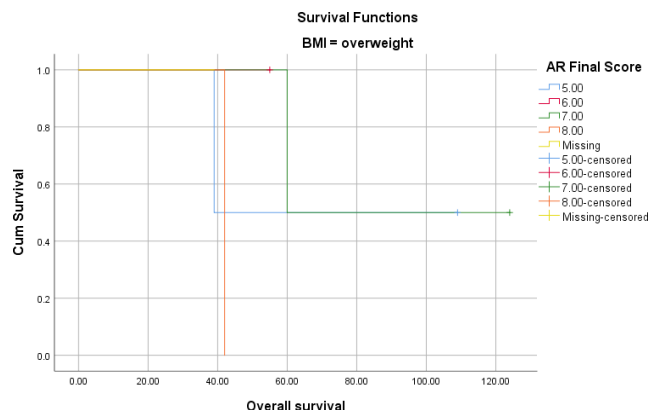


Figure 18: Overall survival in luminal A overweight patients.

This Kaplan-Meier curve (Figure 18) shows the overall survival when comparing the levels of androgen receptor expression in luminal A overweight patients as estimated by Body mass Index (BMI); as follows:

- Score 7: 100% → 60 months... 50% → 125 months
- Score 5: 100% → 48 months... 50% → 110 months
- Score 6: 100% → 55 months
- Score 8: 100% → 43 months (with maximal standard error: 0.354)

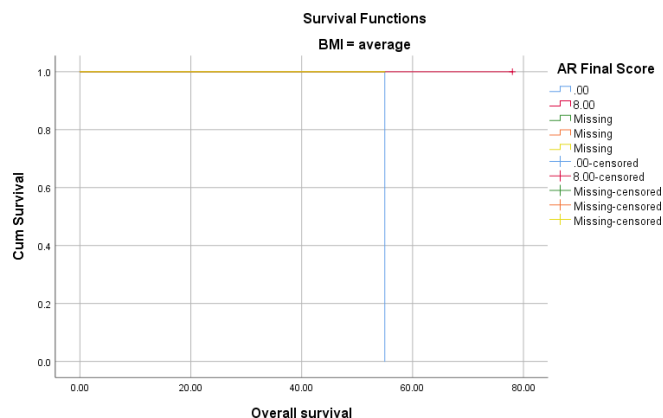


Figure 19: Overall survival in luminal A patients with average Body mass Index.

This Kaplan-Meier curve (Figure 19) shows the overall survival when comparing the levels of androgen receptor expression in luminal A patients with average Body Mass Index (BMI); as follows:

Score 8: 100% → 78 months

- Score 0: 100% → 55 months (with maximal standard error: 0.000)

This Kaplan-Meier curve (Figure 20) shows the overall survival in luminal A underweight patients, as estimated by the Body Mass Index (BMI) as follows:

- Score 6: 100% → 52 months
- Score 3: 100% → 52 months ... 50% → 72 months. (with maximal standard error: 0.354)

With age group:

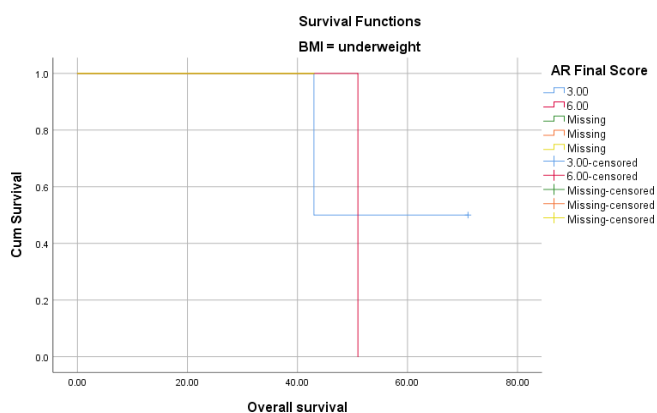


Figure 20: Overall survival in luminal A underweight patients.

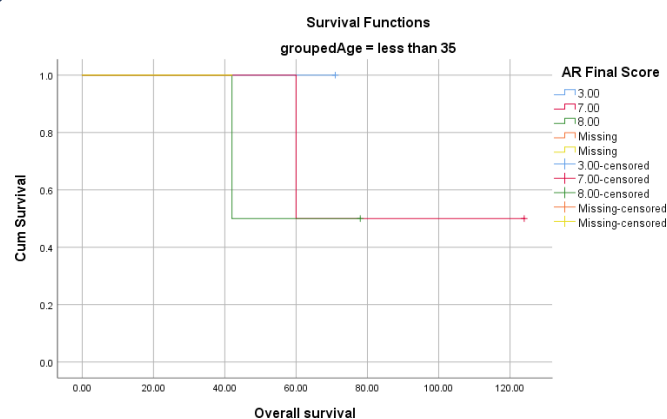


Figure 21: Overall survival in luminal A patients aging less than 35 years.

This Kaplan-Meier curve (Figure 21) shows the overall survival in luminal A patients aging less than 35 years; as follows:

- Score 7: 100% → 60 months... 50% → 125 months
- Score 3: 100% → 72 months
- Score 8: 100% → 42 months... 50% → 78 months. (with maximal standard error: 0.354)

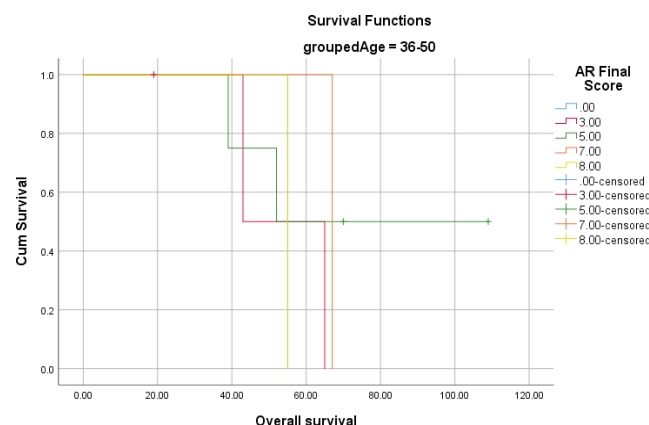


Figure 22: Overall survival in luminal A patients aging 36 to 50 years.

This Kaplan-Meier curve (Figure 22) shows the overall survival in luminal A patients aging 36 to 50 years; as follows:

- Score 7: 100% → 68 months
- Score 5: 100% → 39 months... 75 % → 52 months... 50% → 110 months
- Score 8: 100% → 55 months
- Score 3: 100% → 44 months... 50% → 66 months. (with maximal standard error: 0.354)

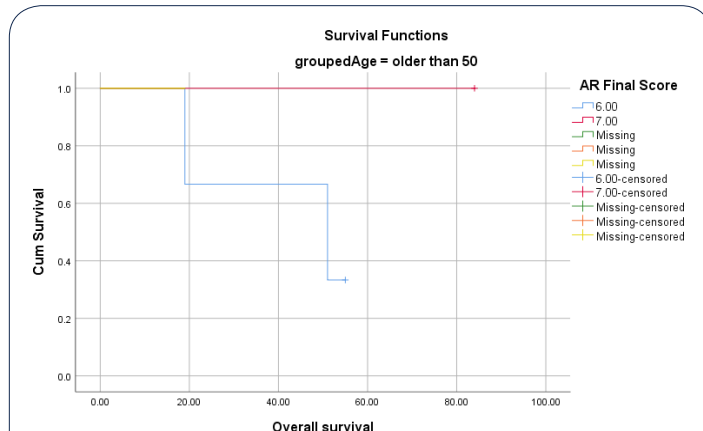


Figure 23: Overall survival in luminal A patients aging older than 50 years.

This Kaplan-Meier curve (Figure 24) shows the overall survival in luminal A patients aging older than 50 years; as follows:

- Score 7: 100% → 85 months
- Score 6: 100% → 19 months... 68 % → 52 months... 36% → 55 months (with maximal standard error: 0.272)

With menopausal

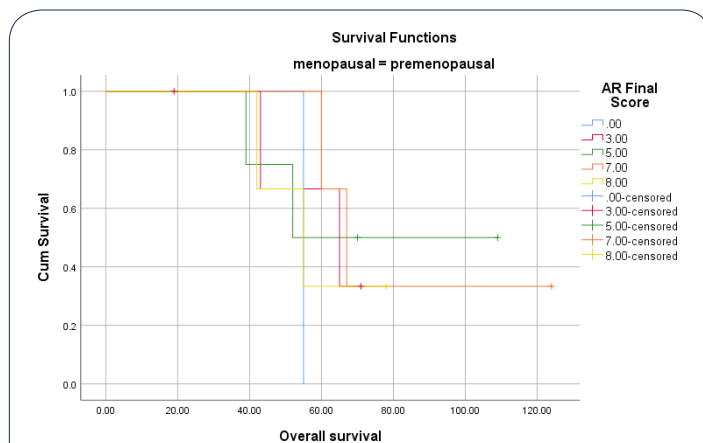


Figure 24: Overall survival in luminal A premenopausal patients.

This Kaplan-Meier curve (Figure 24) shows the overall survival in luminal A premenopausal patients; as follows:

- Score 7: 100% → 60 months... 66% → 68 months... 33% → 125 months
- Score 0: 100% → 56 months
- Score 3: 100% → 44 months... 68 % → 68 months... 35% → 70 months

- Score 5: 100% → 38 months... 75% → 54 months... 50% → 110 months
- Score 8: 100% → 42 months... 68% → 56 months... 36% → 78 months (with maximal standard error: 0.272)

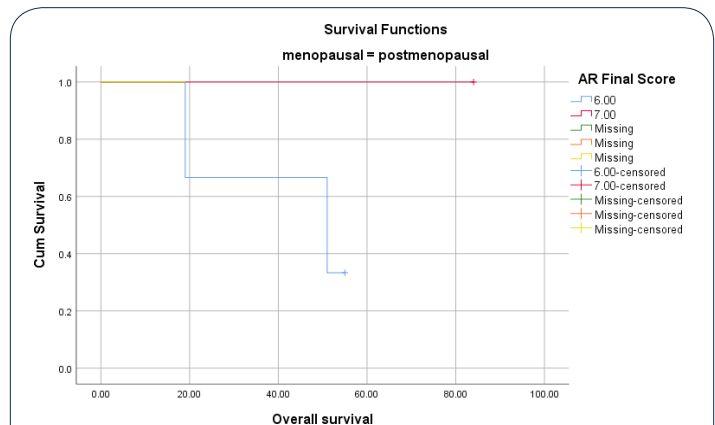


Figure 25: Overall survival in luminal A postmenopausal patients.

This Kaplan-Meier curve (Figure 25) shows the overall survival in luminal A postmenopausal patients; as follows:

- Score 7: 100% → 85 months
- Score 6: 100% → 18 months... 68% → 52 months... 34 % → 55 months (with maximal standard error: 0.272)

With stage early versus advanced

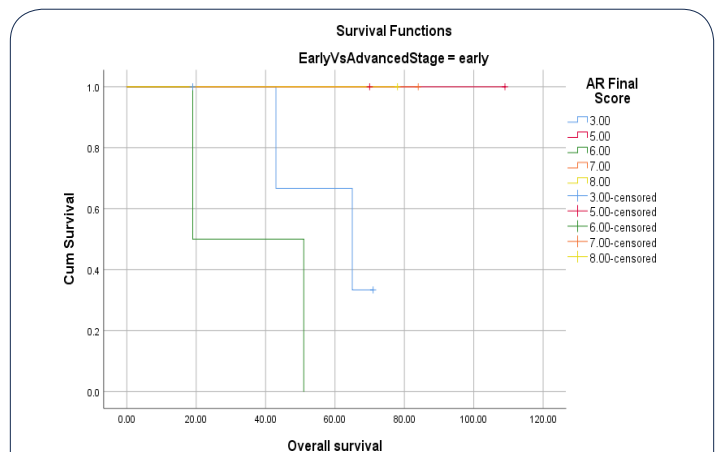


Figure 26: Overall survival in luminal A patients with early stage.

This Kaplan-Meier curve (Figure 26) shows the overall survival in luminal A patients with early stage; as follows:

- Score 5: 100% → 110 months
- Score 8: 100% → 78 months
- Score 3: 100% → 44 months... 68 % → 68 months... 35% → 70 months
- Score 6: 100% → 19 months... 50% → 52 months (with maximal standard error: 0.354)

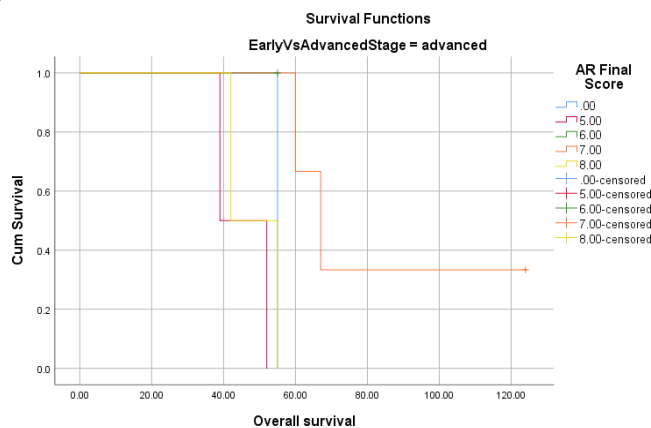


Figure 27: Overall survival in luminal A patients with advanced stage.

This Kaplan-Meier curve (Figure 27) shows the overall survival in luminal A patients with advanced stage; as follows:

- Score 7: 100% → 60 months... 66% → 68 months... 33% → 125 months
- Score 0: 100% → 56 months
- Score 8: 100% → 42 months... 50 % → 68 months
- Score 5: 100% → 38 months... 50% → 60 months (with maximal standard error: 0.354)

Summary of OS curved of luminal A subgroup

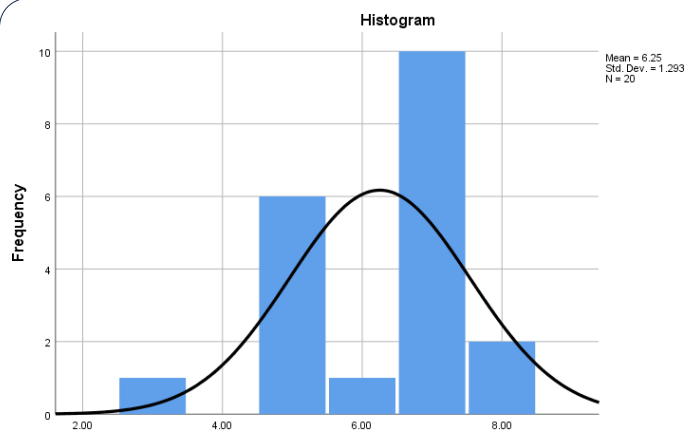


Figure 28: Score 5 androgen receptor expression is the predominant and has the overall survival (OS) in all luminal A patients.

This histogram (Figure 28) shows that score 5 as degree of androgen receptor expression is the predominant and has the Overall Survival (OS) in all luminal A patients in our study. Z score = -17.96. P-Value is <.00001. (statistically significant)

Discussion

❖ Vera-Badillo FE in 2014 found -in a large systematic review that included 7693 breast cancers among 19 studies- that AR expression was 74.8% in ER- positive tumors and 31.8% in ER-negative tumors [17].

❖ AR was shown to be expressed up to 90% of ERα positive BC [5].

➤ Here, in our study, 50 (96.1%) out of all our 52 hormonal receptor positive patients stained positive for androgen receptor.

✚ Our results came in concordance with was stated by Giovenalli P and in contradiction with what was stated by Vera-Badillo FE.

❖ Hickey TE and colleagues had published in 2012 that AR might be a potential tumor suppressor in ER-positive breast cancer, with anti-proliferative effects due to cross talk between the steroid receptor signaling pathways [8].

❖ Cochrane and colleagues had demonstrated inhibition of both dihydrotestosterone-mediated and estradiol-mediated proliferation of ER- positive and AR-positive breast cancer cells by antiandrogens [1].

➤ In our study, intermediate androgen receptor expression (score 5) had the best time to both tumor progression and overall survival in all hormonal receptor positive. (P-Value <0.00001) (statistically significant)

✚ Our study results came in agreement with what was stated by Hickey TE, Cochrane and their colleagues.

❖ In 2014, Rechoum Y studied ER-positive breast cancer cells in vitro to investigate variable molecules and the efficacy of variable treatment options. His study showed that: In ER-positive MCF-7 cells engineered to overexpress aromatase and AR (MCF-7 AR Arom cells) treated with Androstenedione (AD), the steroidal AI, anastrozole (Ana) does not inhibit growth and ER transcriptional activity. This effect could be due to an increase in pAKT (phosphorylated AKT, AKT is an oncogene; also known as protein kinase B "PKB") and pIGF-1R levels as well as to a co-operation between AR and ER that might induce the up-regulation of AR and ER-responsive gene expression. AR antagonists, or the antiestrogen fulvestrant or the IGF-1R and AKT inhibitors restore the sensitivity to Anastrozole [14].

❖ He also concluded that AR is also responsible for the Aromatase Inhibitor (AI) resistance in ER-positive BC cells [14].

➤ In our study, Letrozole effect has been shown to be better with the intermediate androgen receptor expression followed by the high levels of androgen receptor expression.

✚ As both are reversible aromatase inhibitors, this finding comes in concordance with what was found by Rechoum Y.

❖ In December 2020, Krob I and the investigating team conducted a randomized Placebo Controlled Phase II Trial Evaluating Exemestane with or without Enzalutamide in Patients with Hormone Receptor-Positive Breast Cancer and concluded that PFS was not improved by the addition of enzalutamide to exemestane in hormone receptor positive androgen receptor positive breast cancer patients [10].

➤ In our study, Letrozole effect has been shown to be better with the intermediate androgen receptor expression followed by the high levels of androgen receptor expression.

✚ This finding came in contradiction with what was found by Krob I.

❖ Kevin H. Kensler and his colleagues stated that an AR:ER ratio ≥ 2 was associated with an increased rate of tamoxifen failure in a cohort of 192 women with ER+ breast cancer [9].

➤ In our study, among breast cancer female patients who received Tamoxifen, positive androgen receptor negatively affected their response to Tamoxifen. The high levels of expression of androgen receptor had the worst response to Tamoxifen. The intermediate degree of expression of androgen receptor had the best prognosis.

✚ Our study results came in concordance with what was stated by Kevin H. Kensler and his colleagues.

Conclusion

Androgen receptor intermediate expression had the best prognosis in luminal A, invasive breast cancer female patients.

Concerning breast cancer female patients who received Tamoxifen, positive androgen receptor negatively affected their response to Tamoxifen. The high levels of expression of androgen receptor had the worst response to Tamoxifen. The intermediate degree of expression of androgen receptor had the best prognosis.

Accidentally, Letrozole effect had been shown to be better with the intermediate androgen receptor expression followed by the high levels of androgen receptor expression. The intermediately positive androgen receptor breast cancer female patients had best response when compared to the highly positive androgen receptor ones.

References

1. Cochrane DR, Bernales S, et al. Role of the androgen receptor in breast cancer and preclinical analysis of enzalutamide. *Breast Cancer Res.* 2014; 16: R7.
2. De Amicis F, Thirugnansampanthan J, Cui Y, Selever J, Beyer A, Parra I, et al. Androgen receptor overexpression induces tamoxifen resistance in human breast cancer cells. *Breast Cancer Res Treat.* 2010; 121: 1-11.
3. Hilborn E, Gacic J, Fornander T, et al. Androgen receptor expression predicts beneficial tamoxifen response in oestrogen receptor- α -negative breast cancer. *Br J Cancer.* 2016; 114: 248-255.
4. De Amicis F, Thirugnansampanthan J, Cui Y, et al. Androgen receptor overexpression induces tamoxifen resistance in human breast cancer cells. *Breast Cancer Res Treat.* 2010; 121: 1-11.
5. Giovannelli P, et al. The androgen receptor in breast cancer. *Front Endocrinol.* 2018; 9: 492.
6. Gucaip A, et al. Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic breast cancer. *Clin Cancer Res.* 2013; 19: 5505-5512.
7. Helwick C. Targeting the androgen receptor in breast cancer. *ASCO Post.* 2017.
8. Hickey TE, et al. The androgen receptor in breast tissues: growth inhibitor, tumor suppressor, oncogene? *Mol Endocrinol.* 2012; 26: 1252-1267.
9. Kensler KH, et al. Prognostic and predictive value of androgen receptor expression in postmenopausal women with estrogen receptor-positive breast cancer: results from the Breast International Group Trial 1-98. *Breast Cancer Res.* 2019; 21: 42.
10. Krob I, et al. A randomized placebo-controlled phase II trial evaluating exemestane with or without enzalutamide in patients with hormone receptor-positive breast cancer. *Clin Cancer Res.* 2020; 26: 6149-6159.
11. Lebert JM, et al. Advances in the systemic treatment of triple-negative breast cancer. *Curr Oncol.* 2018; 25: 119-128.
12. Park S, et al. Expression of androgen receptors in primary breast cancer. *Ann Oncol.* 2010; 21: 488-492.
13. Raosoft Inc. Sample size calculator. Raosoft. 2004.
14. Rechoum Y, Rovito D, Iacopetta D, Barone I, Andò S, Weigel NL, et al. AR collaborates with ER-alpha in aromatase inhibitor-resistant breast cancer. *Breast Cancer Res Treat.* 2014; 147: 473-485.
15. Rizza P, Barone I, Zito D, Giordano F, Lanzino M, De Amicis F, et al. Estrogen receptor beta as a novel target of androgen receptor action in breast cancer cell lines. *Breast Cancer Res.* 2014; 16: R21.
16. Suez Canal University Clinical Oncology Department. Confidential archive files. Ismailia: Suez Canal University; 2008-2022.
17. Vera-Badillo FE, et al. Androgen receptor expression and outcomes in early breast cancer: a systematic review and meta-analysis. *J Natl Cancer Inst.* 2014; 106: djt319.