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Review Article

A Critical Review on The Impact of Aging on Development and Prognosis, Diagnosis, And Treatment of Epithelial Ovarian Cancer in The Elderly

[1]Shittu MA, [1]Olaoye SO, [1]Danladi Abubakar

[1]Department of Obstetrics and Gynaecology, Federal Medical Centre, Gusau.

ABSTRACT

There would be a significant rise in the number of older women globally and this increase is expected to continue exponentially in decades to come. Older women are those aged 65 years and above, and they have higher cancer incidence and mortality rates relative to their younger counterparts. Most epithelial ovarian cancers occur in older women and chronic inflammation, age-related genetic aberrations and the impact of endogenous and exogenous stimuli including viruses are thought to play significant roles in the aetiologic processes that lead to the development of epithelial ovarian cancer. The diagnosis of ovarian cancer is difficult and age-related frailty and poor performance status in this category of patients make the choice of available treatment difficult.

Corresponding Author:

Shittu Muhammad Adamu
shittumuhd@gmail.com
Contact: +2348039492682

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INTRODUCTION

Epithelial ovarian cancer ranks seventh among cancers in women and accounts for nearly 5% of all newly diagnosed cancers in women globally [1, 2] Around 50% of patients with epithelial ovarian cancer present above the age of 65 years and over two-thirds of deaths from this condition occur in this age group [3]. With the increase in life expectancy, the number of older women with epithelial ovarian cancer will continue to be on the increase, and these category of patients are less likely to receive aggressive surgical treatment or chemotherapy, are prone to developing increased toxicity from chemotherapy, and have poorer prognosis compared to their younger counterparts [4, 5]. These patients are also under-represented in clinical trials and therefore the introduction of a conventional treatment regime in them can be a great challenge [6]. Performance status and age are inadequate tools to

predict the toxicity of older patients from chemotherapy [2].

IMPACT OF AGING ON EPITHELIAL OVARIAN CANCER AND PROGNOSIS

In many decades to come, the prevalence of cancer will continue to rise rapidly globally, especially in developed countries and these numbers will continue to add to the difficulties of already existing cases awaiting treatment 6. Ovarian cancer affects the elderly and around 50% of the cases are diagnosed after the age of 65 years and nearly 70% of the mortality from the condition occurs in this group of patients [5].

Women of advanced age experience an age-related increased activity of the mammalian target of rapamycin (mTOR)[7] and the mTOR/ phosphatidylinositol-3 kinase (Pi3K) signal pathway [8]. This pathway is a major regulator of cellular proliferation and its dysfunction is thought to contribute to the oncogenic processes leading to epithelial ovarian cancer (EOC) [9]. The activation of the mTOR signal occurs as a result of the deletion of lkb, TSC1 and TSC2 genes in the ovarian surface epithelium (OSE) leading to hyperplasia and epithelial ovarian carcinoma, but not stromal cell cancers [10]. The mTOR activity is cell-type specific rather than organ-specific in its role in the age-related pathogenesis of EOC [5, 8]. Additionally, EOC triggers both local and systemic inflammatory responses and within this milieu, cells of the immune system such as epithelial cells, macrophages and fibroblasts release mediators of inflammation like interleukin 8 (IL8), Interleukin 6 (IL6) and Tumour Necrosis Factor (TNF) [11, 12]. The serum level of these markers is associated with poor survival in aged patients with EOC [11, 12]. However, the inflammatory response may not be the aftereffect of the EOC, but rather the cause [13].

Evidence has shown that as age advances, the body enters into a phase of a chronic inflammatory process referred to as "inflammageing" [14] and the chronicity of the process rather than the magnitude fuels the "inflammageing" [13]. This age-associated phenomenon has both endogenous and exogenous stimuli including infections with Cytomegalovirus Epstein Barr virus [15]. A group of retrotransposons, referred to as LINE-1 elements are stimulated with ageing resulting in damage to DNA and the build-up of genetic aberrations [16]. Furthermore, there is an emergence of senescent cohorts of cells in organs of the body as well as the immune system 17 with further build-up of damaged DNA. The senescent cells metamorphose to a Senescent-Associated Secretory Phenotype (SASP) that releases excessive levels of mediators of inflammation and cytokines [17]. Over time, the immunosurveillance function declines to lead to the accumulation of senescent cells and a prolonged chronic inflammatory state. SASP are believed to be pro-carcinogenic as they create inflammatory foci that could provoke the formation of malignant cells [18] and this has been described with EOC [13].

The overall survival (OS) of elderly patients with EOC is poor irrespective of stage and the 5-year survival was reported as 58.8% compared with 78.8% in the younger patients [19]. The OS decreases with advancing age and becomes worse in the elderly with advanced-stage disease [20]. An age-stratified survival report indicated a survival rate of 57% for cases between 65 and 69 years, 45% for 70 to 75 years and 33% for patients between 80 and 84 years [21]. The reason for the poor outcome has not been clearly explained. Telomere length (TL) is believed to be an indicator of prognosis in older patients with advanced epithelial ovarian cancer (AEOC)[22]. The ageing processes induce a continuing reduction in functional reserve which negatively affects cancer treatment as telomere length shortening enhances tissue senescence and frailty[23] because of its relationship with the risk of medical morbidities which affect treatment outcome. Telomere length shortening was demonstrated to correlate with OS in EOC [24].

This observation was thought to be of minimal clinical utility since its predictive relevance in individual patients with EOC is poor[22]. Notwithstanding, another report suggested an unambiguous correlation with prognosis, and it identified a cohort of elderly patients with short TL at risk of receiving incomplete treatment, severe adverse reactions and emergency admission to hospitals[25]. However, the application of this finding in the clinical scenario might be challenging and the assignment of TL being short or long depends solely on technicalities and the population examined and TL is also less reliable than geriatric vulnerability score at predicting survival[5].

It was reported that advanced age is associated with late-stage presentation and

potentially aggressive tumours [20]. However, a study revealed that the disparity in survival between the elderly and the young was only noticeable in the first year after diagnosis than 5 years, implying older patients who survived after 1 year have a similar prognosis compared to younger counterparts[20]. Zhang and colleagues[26] indicated that the prevalence of p53 mutation increases with advancing age, and TP53 dysfunction was confirmed in almost 100% of high-grade serous ovarian cancers (HGSOC)[27], and over 80% of EOC occurs in the elderly[26]. Pathogenic P53 mutation was also described as the earliest event in the process leading to carcinogenesis[26]. P53 autoantibodies were detected in 20-24% of patients with EOC FIGO stage 3 and 4[28], but the role of this in the detection of ovarian cancer in the early stage has not been authenticated[26]. As a prognostic marker for survival, P53 has shown inconsistent results.

DIAGNOSIS

Clinicians have indicated that ovarian cancer does not present with symptoms in its early stage[29]. Notwithstanding, symptoms of the early disease may be obvious, and most times interpreted as less serious complaints and as a result, many patients delay seeking medical help[30]. Despite most cases of EOC presenting this way, gastrointestinal manifestations, urinary tract symptoms, abnormal vaginal bleeding and wasting were reported symptoms before diagnosis and as such almost 30% of patients are diagnosed early[30]. In contrast to the expectation of most clinicians, elderly patients with ovarian cancers have symptoms. Among them, fatigue and urinary symptoms were the most frequent complaints associated with the early stage but only irregular vaginal bleeding often compelled the elderly to seek medical help[31]. Over 50% of elderly patients with AEOC present with fatigue and this is a common complaint in elderly adults who may not necessarily have any malignancy[31]. A report from a nursing home (average age 88 years) indicated that almost 40% and 7% of inhabitants had moderate to severe fatigue respectively as determined by a valid scoring scale[32]. In comparison, elderly patients with advanced disease commonly present with pain and abdominal distension 31, and the pain was reported to be the main reason for seeking medical assistance[33]. There was no evidence of changes in perception of pain in the elderly but only 13% of elderly patients experiencing regular pain receive any form of analgesia compared with 38% in those 65 to 74 years, it was noticed that African American women and those with poor cognitive function were less likely to demand pain relief[29].

Ultrasound scan is the modality of choice for the evaluation of elderly patients with ovarian lesions because it minimizes the risk of exposure to radiation and functions as a safer alternative to CT-scan and MRI[34]. There are several challenges with the use of ultrasound in elderly patients with ovarian cancer. Although abdominal ultrasound allows evaluation in the elderly, it is not devoid of difficulties as the investigation may be compromised by many senescent changes such as reduced bladder capacity and distorted habitus 35. This category of patients has decreased bowel peristalsis with resultant accumulation of intestinal luminal gases which negatively affects image qualities. Furthermore, free gas and ascitic fluid might be present in cases receiving peritoneal dialysis[35]. Sonographic echogenicity is also enhanced due to tissue fibrosis and calcification and formation of plaques in the vasculature leading to artefact formation and poor image quality[36]. Therefore, presurgical ultrasound characterization of ovarian cancer presents a unique diagnosis difficulty and this has enormous consequences on treatment approach, survival and prognosis[37]. Transvaginal scan (TVS) has been a useful tool in the elderly and despite the atrophic changes in the vagina, there was high acceptance and tolerance to TVS among elderly patients than in younger patients[38]. Bimanual pelvic examination and cancer antigen 125 (CA-125) values have failed to distinguish benign from malignant ovarian lesions[39]. Ultrasound scan as a preferred modality has a 65-95% accuracy[7], 88 to 96% sensitivity and 65-94% specificity[37].

The structural changes that differentiate benign from malignant tumours; like an irregular thick wall, papillary excrescences, septations, and solid echogenic areas are features of a malignant lesion[40]. The risk of malignancy index is a scoring system that is obtained from the product of the scores of features on TVS, scores as 1 for each feature, 3 for the postmenopausal status of the elderly patient and the CA-125 values. A score above 200 is highly suggestive of ovarian cancer[40]. Although ultrasound is useful for the diagnosis of ovarian cancer, it is not reliable for staging the

disease. Incorporation of Doppler interrogation may be complementary when results are equivocal 37, but another view suggested it may add minimal additional findings[41].

The morphologic scoring index which is a cheap, reproducible and accurate tool of evaluation is useful in distinguishing benign from malignant lesions and is valuable in determining which category of patients would require surgical debulking[41, 42]. It is particularly useful in detecting malignant ovarian lesions in the elderly[40, 41].

The score is derived from the following tumour features: volume, wall, septation, and extra-tumoral free fluid (Figure 1). The ovarian volume is calculated using the prolate ellipsoid formula (length x width x height x 0.523) and a score of 0 to 5 is assigned to each tumour parameter and 0 to 10 for tumour[43]. (Table 1).

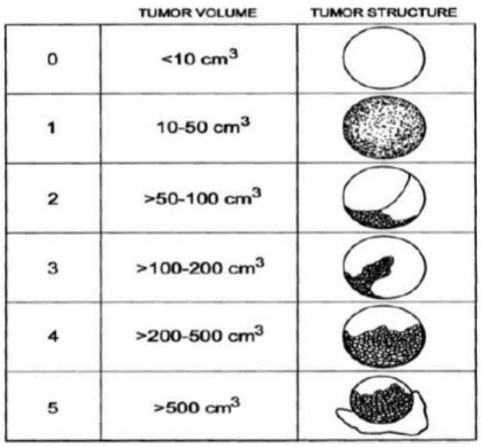

Figure 1. Pictorial representation of morphologic index for ovarian lesions. Copied from Ueland *et al.*[30].

Table1. Sonographic morphologic index for ovarian lesions

	Category					
	0	1	2	3	4	5
Vol. (cm^3)	<10	10-50	>50-100	>100-200	>200-5000	>500
Structure	Smooth wall, sonolucent	Smooth wall, Diffuse echogenicity	Wall thickening, <3mm	Papillary projection >3mm	Complex, predominantly solid	Complex, solid and cystic areas with extra-mural fluid

Copied from Ashwarya et al.[32]
Calculated using ellipsoid formula (LxWxHx0.523

A score ≥5 has a positive predictive value of 0.450 for malignancy in the elderly compared with 0.138 in the younger patients[40]. The scores of morphologic indexing were noticed to bear no significant relationship with the age of the patients. Table 2 describes the characteristics of some primary research on morphologic score indexing.

Table 2. Characteristics of primary studies on morphologic indexing of ovarian tumours

Author	year	No. of patient	Country	Prevalence of malignancies	Cut-off score	Accuracy for Stage 1 cancer (%)	Sensitivity (%)	Specificity (%)
Aishwarya *et al.*[32]	2017	136	India	30		68	95	56
DePriest *et al.*[29]	1993	121	USA	10		44	89	70
Ferrazzi *et al.*[33]	1997		Italy	20		-	75	67
Granberg *et al.*[34]	1991	180	Sweden			52	82	92
Lerner *et al.*[35]	1994	312	USA	19		63	97	77
Sassone *et al.*[31]	1991	143	USA	28.6		65	100	83
Yamashita *et al.*[36]	1997	115	Japan	43.5		87	85	78
Ueland *et al.*[30]	2003	442	USA	12		82	53	78

Table 3. Distribution of risk factors and postoperative complications in elderly patients[44]

	Postoperative Compli-cations		
Type of procedure	Yes	No	P value
Standard	4	30	0.27
Radical	18	62	
Supraradical	7	19	
Elderly			
Yes	16	61	1.0
No	13	50	
Major morbidity			
Yes	11	58	0.21
No	18	53	
Previous laparotomy	14	46	0.53
Yes	14	65	
No			
Stage			
I and II	4	24	0.44
III and IV	35	87	
Transfusion			
Yes	14	38	0.20
No	15	73	

There was no significant relationship between postoperative and elderly age, comorbidity and previous laparotomy.

The risk of detecting an underlying malignancy varies from 0.3% with a score of <5[40] to 87.2% with a score > 7 across the studies[41]. The diagnostic accuracy in detecting ovarian cancer[44-47] at an early stage varies from 52 to 87% (Table 2). Despite wide ranges of sensitivity and specificity, the findings from the studies indicated that morphologic index assessment before surgical

debulking can identify ovarian lesions at high risk of malignancy for appropriate referral to an oncological surgical unit[48].

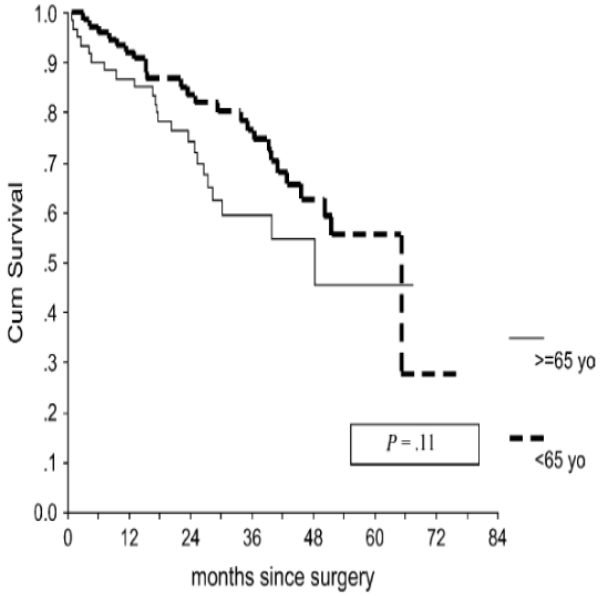

Figure 2. Survival curve shows elderly patients have similar overall survival as younger patients (p=0.11). Copied from Sharma et al.[44]

Table 4. Toxicity in paclitaxel-treated patients based on age group[45]

Toxicity	≤ 70 years (n = 323)	≥ 70 years (n = 74)	p-value
Neutropenia			
All grades	71.5%	74.3%	0.669
Grade	38,8%	48.6%	0.125
Anaemia			
All grades	72.1%	70.3%	0.775
Grade 3,4	5.3%	8.1%	0.522
Thrombocytopenia			
All grades	18.6%	18.9%	1.000
Grade 3,4	2.5%	6.8%	0.071
Allergy			
All grade	3.4%	4.1%	0.731
Grade 3,4	0	2.7%	0.006
Renal			
All grades	2.8%	4.1%	0.474
Grade 3,4	0.7%	0	0.467
Nausea and vomiting			
All grades	57.6%	59.5%	0.795
Grade 3,4	2.1%	1.4%	0.666
Neurotoxicity			
All grades	69.7%	64.4%	0.403
Grade 3,4	2.5%	2.7%	0.925
Neutropenic infection	2.5%	2.7%	0.925
Grade 3,4			

There were no significant differences in recorded adverse events between the 2 age groups except in grade 3 and 4 allergy

Table 5. Summary of treatment-emergent adverse events (TEAEs) and dose reductions, interruption and discontinuation by treatment arm and age[46]

Characteristic	Niraparib (n=367)		Placebo (n=179)	
	Age < 70 (n=306)	Age ≥ 70 (n=61)	Age < 70 (n=145)	Age ≥ 70 (n=34)
Median treatment exposure (days)	250	250	163	163
Median duration of follow-up (months)	17.2	17.3	16.4	16.0
Total number of TEAEs	5950	1132	1300	235
Any TEAE (%)	100	100	95.2	97.1
Any grade ≥ 3 TEAEs (%)	74.8	70.5	22.1	26.5
Any serious TEAE (%)	29.4	32.8	13.8	20.6
Any TEAE leading to death (%)	0	0	0	0
Any TEAE leading to dose reduction (%)	69	68	4.1	8.8
Any TEAE leading to dose interruption (%)	68.6	55.7	15.2	11.8
Any TEAE leading to dose discontinuation (%)	13.7	19.7	2.1	2.9

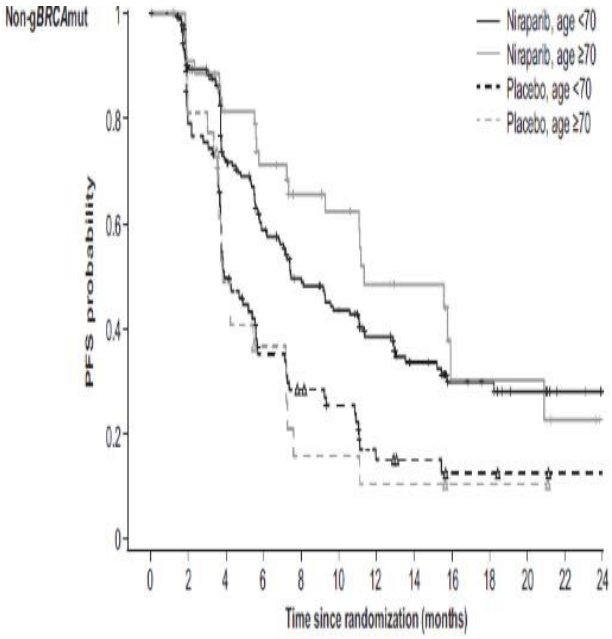

Figure 3. Progression-free survival with niraparib or placebo by age group. Copied from Fabbro et al.[46]

TREATMENT

Ovarian carcinoma is a disease of elderly women and about 50% of the newly diagnosed cases were in patients above 65 years of age 3. The ageing process is accompanied by an increasing incidence of chronic illnesses and continuing decline in functional reserve and resultant haemodynamic

changes that predispose to complications[5]. The alterations in haemodynamic and functional status occasioned by ageing may not be apparent, but when the system is challenged by stressors like surgery and chemotherapy, complications eventually develop[49]. The treatment regime was often derived from results of clinical trials conducted with younger and less frail cohorts administered to the elderly and unwell group of patients[3, 50]. Hence the efficacy and safety of the conventional and novel treatments in older patients with EOC are not well understood.

Before the commencement of treatment, a comprehensive geriatric evaluation is necessary to help detect abnormalities that are often not recognized by routine clinical evaluation. An example is the Geriatric Vulnerability Score (GVS) which assesses albumin, lymphopenia, activities of the daily living score (ADL score), Hospital anxiety and depression scale score (HADS score). A GVS of ≤ 3 is predictive of low OS, lower likelihood of completion of treatment, increased incidence of adverse events and unplanned hospitalization[5].

The best and most favourable therapy for AEOC is primary surgical debulking and subsequent platinum-taxane-based chemotherapy. Elderly patients have a lower frequency of debulking surgery probably due to a higher risk of postoperative death and excessive morbidity 3. A study indicated that overall survival is reduced with advancing age from 3.4 months to 1.6 years for patients aged 65 to 69 years and $\geq$ 80 years respectively, indicating age as an independent prognostic variable for OS [51]. It again suggested that elderly patients with AEOC suffered worse morbidity and mortality and poor tolerance to chemotherapy. However, OS was comparable between the two groups, but the older cohorts had higher rates of suboptimal debulking surgery because they were less likely to endure more complete cytoreductive operations. Likewise, another report revealed that the likelihood of optimal surgical debulking did not depend solely on tumour stage and histology, but also on age, nutritional and functional status [52]. As opposed to this view, Wright and colleagues reported equal rates of cytoreduction among patients less than and above 70 years with no remarkable difference in OS between the two groups[53]. Similarly, another study suggested that patients aged 65 to 75 years and those above 75 years tolerated all forms of radical surgical procedures with outcomes comparable to younger patients[54]. Furthermore, a study[55] in which 45% of participants were $\geq$ 65 years among whom 50% have co-morbidities indicated aggressive optimal debulking was achievable with a lower rate of complications in patients with risk factors (Table 3) Table. Also, the study revealed elderly patients have similar overall survival as the younger patients ($p=0.11$) (Figure 2). The importance of these findings is radical surgery is safe and achievable in the elderly with AEOC and despite the association between age and risk of morbidity, the elderly when carefully selected could benefit from virtually all forms of radical surgical procedures.

Elderly patients with AEOC rarely receive complete doses of chemotherapy because of co-existing morbidities, poor performance status and risk of death[3, 5]. The most common adverse events of chemotherapy are grade 3 or higher toxicities notably haematologic and gastrointestinal[50, 56, 57]. Among a group of elderly patients with AEOC, apart from age, tumour stage and co-existing medical conditions are additional risk factors, but not receiving surgery together with chemotherapy poses a greater risk for poor outcome[58]. Joseph et al.[59] suggested that delaying the administration of chemotherapy is linked to a decrease in survival. However, a dosage reduction of cisplatin-paclitaxel seems equally efficacious and tolerable in the elder with AEOC with no disparity in PFS and OS; and OS between a patient who received standard or reduced dose were 41 months and 44 months respectively[60]. Additionally, Efstathiou et al.[56] indicated patients older than seventy years who received platinum-based chemotherapy have reduced OS compared with younger patients with the OS at 38.8 months and 52.2 months respectively. Age above 70 years was associated with less frequent chemotherapy administration, but toxicity was similar in both groups (Table 4).

As novel targeted therapeutic agents, poly-ADP-ribose polymerase inhibitors have shown remarkable efficacy in EOC patients with BRCA mutation by killing selectively cancer cells with homologous recombination repair deficiency and at the same time sparing normal cell[50]. Olaparib significantly increased PFS to 8.4 months compared with 4.8 months for placebo in patients with recurrent AEOC. Fabbro et al.[57] reported niraparib significantly prolonged PFS in patients $\geq$ 70 years with or without BRCA mutation

and the efficacy and tolerability were comparable to those in younger patients (see table). Also, the median PFS of patients < 70 years treated with niraparib was 7.5 months compared with placebo, while the PFS of those ≥70 years was 11.3 months compared with 3.8 months with placebo (Figure). A recent Randomized controlled trial (RCT) however, indicated Olaparib caused a worse grade 3-4 adverse events among patients ≥ 65 years[50]. The findings from this study should be interpreted with caution since all the patients recruited were above ≥ 65 and have not been separated into a group for comparison. More RCTs using PARP inhibitors are thus required to determine their safety and efficacy in the elderly.

Bevacizumab, a vascular endothelial growth factor monoclonal antibody that suppresses angiogenesis improves PFS both as a first-line, and second-line agent for relapsed AEOC[61]. It was demonstrated to prolong RFS in an RCT in patients less than or greater than 65 years and its use was associated with a higher prevalence of severe hypertension in the elderly compared with younger patients (39% versus 17%) and there was no difference in PFS and OS [62].

CONCLUSIONS

The number of older people diagnosed with cancer and living with epithelial ovarian cancer will continue to rise over time due to improvements in life expectancy and cancer survival. This, therefore, highlights the significance of further studies in older patients with epithelial ovarian cancer to provide effective and rational management. These studies need to include elderly patients that could benefit from active treatment, whereas treatment decisions based mainly on a patient's chronologic age should be avoided. The organization of an oncogeriatric team could improve the proper case selection of high-risk patients ensuring customized treatment.

Disclosure of interests

There are no conflicts of interest.

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