Role of androgen receptor expression in the metastatic potential of colorectal carcinoma

Abd AlRahman Mohammad Foda[a,b], Hader I. Sakr[c,d], Rania M. Sabry[e], Wesal M. Eldehna[f,g], Khaled Abd Elaziz Ahmed Elnaghi[h,i], Eman T. Enan[a]

Departments of [a]Anatomic Pathology, [f]Clinical Oncology and Nuclear Medicine, [h]Oncology Centre, Medical Oncology unit, Internal Medicine Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt, Departments of [c]Medical Physiology, [e]Anatomic Pathology, Faculty of Medicine, Cairo University, Cairo, Egypt, Departments of [b]Pathology, [d]Medical Physiology, General Medicine Practice program, Batterjee Medical College, Jeddah, Saudi arabia, [g]Department of Oncology, International Medical Center, Jeddah, [i]Medical Oncology Department, Oncology Center, King Abdullah Medical City, Makkah, Saudi Arabia

Correspondence to Hader I. Sakr, MD, PhD, Medical Physiology. Postal code: 11562;
Tel: +(002) 011 1161 6364;
fax: +(002) 272-72148;
e-mail: hadersakr@kasralainy.edu.eg

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Background
The prevalence of colorectal cancer (CRC) is widespread and associated with significant morbidity and deaths. In CRC, hormone receptors, such as androgen receptors (AR), are pathologically modified. Additional research is required to understand better its function and predictive and therapeutic value in CRC metastatic potential.
Objective
To assess the AR status in CRC primary tumors and metastatic lymph nodes.
Methods
Tissue microarray and immunohistochemical techniques were applied to 75 CRC cases with lymph node (LN) metastases. We correlate the results with all relevant clinicopathological indicators of prognostic relevance.
Results and conclusion
Out of the 75 cases that were analyzed, 16% of CRC primaries and 12% of LN metastases had nuclear AR that was focally positive. AR expression was significantly correlated with advanced age, conventional non-mucinous histology, lower grade, and arousal on top of adenoma. A deeper invasion was likewise linked to AR expression; however, this association was not statistically significant. AR expression has a positive prognostic influence since the median overall and disease-free survival of cases with positive AR expression in either primary carcinomas or LN metastases were significantly higher than that of cases with negative expression in both primary and LN metastases. We assume that AR expression in CRC has a positive prognostic influence.

Keywords:
androgen receptors, colorectal cancer, metastasis, prognostic, survival

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Introduction

Worldwide, colorectal cancer (CRC) is the second-most significant cause of cancer-related death and the third-most diagnosed malignancy [1]. In the United States, CRC is the third most frequent cancer in terms of both cancer diagnoses and cancer-related deaths for both genders. However, it is the most common cause of death for men under 50 and comes in second place among overall cancer-related causes of death [2]. The prevalence of CRC is rather significant in various Arab nations. In Egypt, CRC represents the ninth most prevalent tumor, with an overall incidence ranging from 0.4% to 14% and a 5-year prevalence of 7.51/100.000/year [3]. In Saudi Arabia and the United Arab Emirates, on the other hand, CRC incidence is 0.72% and 0.78%, respectively, and its prevalence is 7.5/100 000/year in Qatar [4].

CRC has a variety of histopathological types that can be generally classified into nonmucinous adenocarcinoma (NMA) and mucinous adenocarcinoma (MA), which can be either with extracellular mucin lakes (colloid carcinoma) or signet ring cell adenocarcinoma (SRCC) with intracellular mucin and a more aggressive biologic behavior, both have more than 50% of their tumors made up of mucin. The term 'Ordinary adenocarcinoma with mucinous component (OAMC) refers to a tumor if extracellular mucin makes up less than 50% of its mass [5,6].

Regional lymph node (LN) metastasis is implemented in CRC staging and is a predictive factor. When regional LNs are involved, the 5-year survival drops drastically from 60 to 20%. Survival is 60% when one to four LNs are involved and 20% when metastatic deposits involve more than five [7]. Owing to improvements in the management of metastatic

tumors and the establishment and improvement of targeted therapies, the 5-year survival rate for CRC increased from 50% in the middle of the 1970s to 65% from 2012 to 2018 [8].

Targeted therapies are antibodies or medications that inhibit particular proteins crucial for cancer cells' growth and/or survival. Mainly, hormone therapy is one of the modalities of targeted therapy that can be used alone or in combination with other treatments. It has revolutionized the treatment and the patient's survival of localized and metastatic breast, ovarian, endometrial, and prostate cancer [9].

Androgen receptor (AR) is a nuclear receptor formed of an N-terminal domain (NTD), a DNA-binding domain (DBD), a hinge region (HR), and a ligand-binding domain (LBD) that binds to androgens like testosterone and dihydrotestosterone (DHT). Target DNA is bound by the DBD when a ligand binds to the LBD, promoting AR dimerization and translocation to the nucleus [10]. Testosterone is a steroid hormone responsible for spermatogenesis and secondary male sex traits. Some studies indicate that lack of testosterone has a protective effect against CRC. Moreover, the role of AR is widely recognized in prostate cancer. It continues to demonstrate promise as a biomarker and a therapeutic target in breast cancer as well. However, its role in colon carcinogenesis and the modern-day management of patients with diverse cancers remains uncertain [11,12].

Hormonal implications in the management of CRC are not well established. On the other hand, the predictive and therapeutic potential of hormones in CRC remains very promising [11]. Androgen's potential as a prognostic or therapeutic factor in CRC has not yet been thoroughly investigated in the literature. So, the objective of our study is to assess the AR status in CRC patients of various histopathological types with metastatic lymph nodes using tissue microarray and immunohistochemical techniques and to relate the results with all clinicopathological indicators of prognostic relevance.

Patient and methods

Samples

Files of all resected CRC cases from 2007 to 2011 at the Pathology laboratory were revised. Cases with positive LN metastases were selected, and all glass slides of the primary tumor and the LN metastases were revised. Selection criteria were fulfilled in 75 cases. Any case with incomplete clinicopathological data or composed totally of mucin with few epithelial cells was excluded. The Medical Research Ethics Committee members, Institutional Review Board (IRB), Faculty of Medicine, Mansura University, Mansura, Egypt, approved the study with Code No.: R.23.08.2303.

Clinical parameters and histopathological evaluation

All clinical and pathological data of the 75 cases were revised, including age, sex, size, shape, location, diversity, histological type, grade, status of tumor edges, lymphovascular and perineural invasions, lymphocytic and neutrophilic infiltration peri- and intratumoral, number of dissected LNs, depth of invasion (T), number of positive metastatic lymph nodes (N), distant metastasis (M), TNM staging according to the latest WHO classification of colon cancer [13], associated schistosomiasis and infiltration of surgical cut margins.

Tissue microarray construction

Two high-density manual tissue microarray blocks were constructed using a modified mechanical pencil tip technique as previously described by Foda [14]. Four representative cores of 0.8 mm diameter were punched out from the paraffin blocks of each case (two cores from the primary tumor and two from LN metastases). The TMA blocks also included 34 adenomas and 34 normal colonic mucosa cores. Sections from TMA blocks were prepared for routine H and E and immunohistochemistry.

Immunohistochemistry

Immunohistochemical staining was performed at UCL Advanced Diagnostics, London, UK. For immunohistochemical analysis, 4 μm paraffin sections underwent automated dewaxing and peroxidase blocking using Leica Bond Dewax AR9222. Automated antigen retrieval was then performed on the sections. Leica Bond ER2 Cat. No. AR9640 (pH9) was applied, and the slides were heated to 100°C for 30 min. The primary antibody (Androgen Receptor mouse mAb: NCL-AR-318 Novocastra) was then applied and incubated at ambient temperature for 15 min. The slides were then applied to the rabbit-anti-mouse secondary antibody (Leica Bond Refine detection kit; Cat. No. DS9800). Signal visualization was performed using Bond Polymer (Anti-rabbit Poly-HRP-IgG) for 8 min. DAB (Bond Refine detection kit) was applied for 10 min, and 0.5% copper sulfate was applied for 5 min. Cell nuclei were counterstained with hematoxylin. The Leica Bond Polymer Detection

Kit (DS9800) was used for blocking, visualization, and counterstaining peroxidase. Bond Wash (AR9590) and demineralized water were used for washing steps between reagent steps. The authors performed a semi-quantitative evaluation of the immunostained slides blindly and independently. Positive nuclear staining for AR was reported for each core, either from the primary tumor or the LN metastases. Nuclear staining in greater than or equal to 5% of tumor cells for AR was considered positive [15].

Statistical analysis

Data were analyzed using SPSS, version 24.0 for Windows (SPSS Inc, IBM, Chicago, Illinois). χ^2 was used to test significant differences in categorical variables between various groups. A comparison of survival curves was carried out using the log-rank test. A 2-tailed P less than or equal to 0.05 was considered significant in all tests.

Results and discussion

Clinicopathological and histological features of colorectal carcinoma (CRC) and androgen receptors (AR) cases

Selecting an effective treatment plan for CRC while using different treatment methods is essential. The most effective CRC treatment plan must eliminate the primary tumor and any metastases [16]. Despite the growing understanding of the molecular and cellular elements of CRC, targeted therapy, which aims to treat specific abnormalities in cancer cell biology, is the main focus of research [17]. Androgen's potential as a predictive or therapeutic factor in CRC has not yet been adequately explored. Our study aims to determine the AR status in CRC patients with metastatic lymph nodes and investigate its prognostic value.

In our study, a total of 75 CRC cases and their corresponding LN metastases were analyzed. Ages ranged from 20 to 78 years (mean, 50.6 years, SD=13.6). The patients were 50 males and 25 females, with a male-to-female ratio of 2 : 1. The detailed clinicopathological and histological features of the cases are listed in Tables 1 and 2.

Androgen receptor (AR) expression in colorectal carcinoma (CRC) and corresponding lymph nodes (LN) metastases

All adenomas and normal colonic tissues were negative for AR. Nuclear AR was focally positive in 12 (16%) CRC primaries out of the 75 analyzed cases and in 9 (12%) LN metastases. A total 50% of the cases with positive AR in the primary tumors showed corresponding positivity in the LN metastases. In contrast, about 95% of the cases with negative AR in the primary tumors showed corresponding negativity in the LN metastases (χ^2=19.535, P<0.001) (Table 3 and Fig. 1).

In the current study, all adenomas and healthy colonic tissues tested negative for AR, keeping with Brentani and colleagues' study [18]. Other studies detected that

Table 1 Clinico-pathological features of 75 cases of colorectal carcinoma

	Age (year)		Sex		Location			
	< 40	≥40	Male	Female	Rt side	Lt side	Recto-sigmoid	Trans. colon
Number (%)	21 (28.0)	54 (72.0)	50 (66.7)	25 (33.3)	15 (20.0)	9 (12.0)	49 (65.3)	2 (2.7)
	Tumor size		Multiplicity		Invasion depth		Surgical cut margins	
	< 6	≥6	Negative	Positive	T1/T2	T3/T4	Free	Infilt.
Number (%)	38 (50.7)	37 (49.3)	69 (92.0)	6 (8.0)	4 (5.3)	71 (94.7)	71 (94.7)	4 (5.3)
	TNM stage		LN		Gross picture			
	I /II	III /IV	N1	N2	Fungating	Ulcerating	Annular	
Number (%)	1 (1.3)	74 (98.7)	34 (45.3)	41 (54.7)	22 (29.3)	28 (37.3)	25 (33.3)	

Table 2 Histological features of 75 cases of colorectal carcinoma

	Perineural invasion		Associated adenoma		Associated schistosomiasis		Tumor margins	
	Negative	Positive	Negative	Positive	Negative	Positive	Budding	Pushing
Number (%)	40 (53.3)	35 (46.7)	41 (54.7)	34 (45.3)	63 (84.0)	12 (16.0)	70 (93.3)	5 (6.7)
	Microscopic abscess formation		Intra-tumoral lymphocytic response		Peri-tumoral lymphocytic response (Crohn-like)		Lymphovascular emboli	
	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive
Number (%)	38 (50.7)	37 (49.3)	72 (96.0)	3 (4.0)	60 (80.0)	15 (20.0)	0	75 (100)

Table 3 Androgen receptors expression in 75 lymph nodes metastatic tumors in comparison to their primaries (chi-square= 19.535, *P*<0.001)

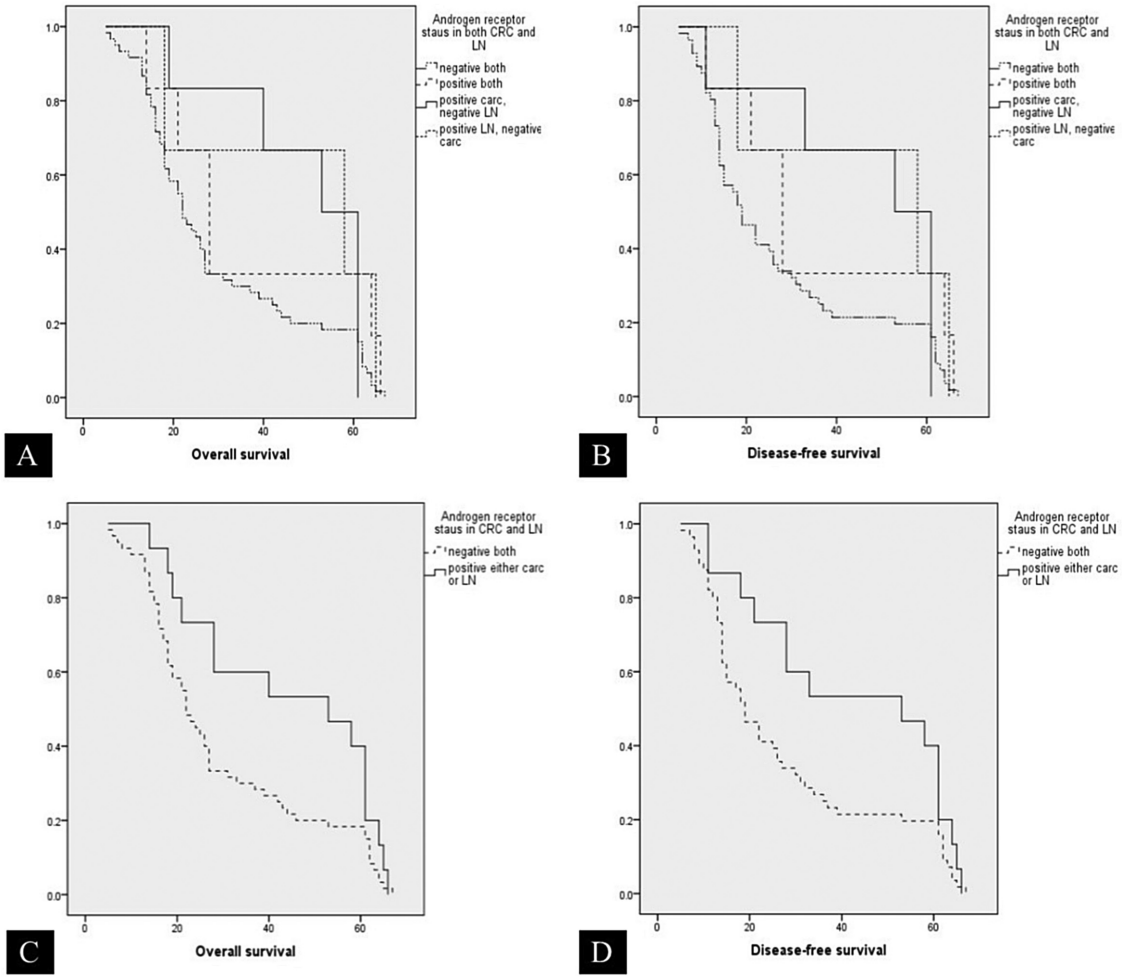
	Lymph nodes	
	Negative (*N*=66; 88.0%)	Positive (*N*=9; 12.0%)
Primary tumors		
Negative (*N*=63; 84.0%)	60	3
Positive (*N*=12; 16.0%)	6	6

81.3% of noncancerous mucosa positively expressed AR [19], or it was completely absent in healthy colonic mucosa, whereas it was present (40%) in colorectal adenoma cases [20]. Wenxuan and colleagues [21] found that AR mRNA is expressed in colon mucosa, either normally or neoplastic, although AR-A expression is only kept up at the protein level in CRC. This controversy might be due to various demographic criteria, techniques, antibody clonality, and material manufacturing techniques.

Relation of androgen receptors (AR) expression with clinicopathological and histological parameters in colorectal carcinoma (CRC) cases and corresponding lymph nodes (LN) metastases

In CRC cases, AR expression was significantly associated with old age (*P*=0.018), conventional non-mucinous histology (*P*=0.001), lower grade (*P*<0.001), and arousal on top of adenoma (*P*=0.024). AR expression was also associated with less depth of invasion but was not statistically significant (*P*=0.057). Neoplastic tissues in males showed slightly more AR expression than in females

Figure 1



Androgen receptors expression in primary and metastatic colorectal carcinoma; A: Positive androgen receptors expression in primary nonmucinous colorectal carcinoma. B: Negative androgen receptors expression in primary mucinous colorectal carcinoma. C: Positive androgen receptors expression in metastatic nonmucinous colorectal carcinoma. D: Negative androgen receptors expression in metastatic signet ring colorectal carcinoma.

(58.3% vs. 41.7%, respectively). Statistically, there was no correlation between gender and AR expression in CRC cases (P=0.504) (Table 4). On the other hand, AR expression in LN metastases was not associated with any of the tested clinicopathological and histological parameters except with histological type. In LN metastases, AR expression was significantly related to conventional non-mucinous histology (P=0.002) (Table 5).

Few previous studies investigated AR expression in CRC and LN metastases and revealed variable results. Our study demonstrated that nuclear AR was focally positive in 16% of CRC primaries and 12% of metastatic LNs. Most tumor biopsies studied by Brentani and colleagues [18] were negative for AR. On the contrary, Albasri and Elkablawy's [20] detected AR in all CRC specimens with varying degrees of positivity, but they considered cytoplasmic staining positive. Refaat and colleagues [22] noticed that the non-neoplastic colonic epithelium had cytoplasmic and nuclear localization of AR, but compared with noncancerous samples, AR protein expression was considerably higher in colonic malignant tissues.

In the metastatic model, tumor cells within primary tumors acquire the ability to metastasize through progressive mutations, implying that metastases are genetically distinct from their parent tumors [7]. To our knowledge, our study is the first to investigate AR expression in metastatic LN tissues. In contrast, previous studies only related AR expression in primary tumors to the potential of LN metastasis as one of the clinicopathological factors of CRC patients. The association between AR expression in 75 LN metastatic tumors compared with their primaries was significant in our studied cases (P<0.001). Fifty percent of the cases with positive AR in the primary tumors showed corresponding positivity in the LN metastases.

In contrast, about 95% of cases with negative AR in the primary tumors showed corresponding negativity in the LN metastases. Similar results were obtained by Albasri and Elkablawy [20] in contrast to Huang and colleagues [19], who noted that there is no significant relation between AR expression in primaries and the possibility of LN metastases. Our results are in line with a previous study that investigated AR expression in breast carcinoma and stated that there was no discernible variation in the expression of the androgen receptor between original breast tumors and corresponding metastatic LNs [15].

Survival of colorectal carcinoma (CRC) patients with lymph node (LN) metastases and relation of androgen receptors (AR) expression to survival

The detailed univariate analyses of significant clinicopathological and histological parameters in patients with CRC and LN metastases concerning

Table 4 Characteristics of androgen receptor expression in 75 cases of colorectal carcinoma

	AR expression			
	Negative	Positive	Chi-square (χ^2)	*P* value
Age *n* (%)				
<40 years	21 (33.3)	0	5.556	**0.018***
≥40 years	42 (66.7)	12 (100.0)		
Sex *n* (%)				
Male	43 (68.2)	7 (58.3)	0.446	0.504
Female	20 (31.8)	5 (41.7)		
Histological type *n* (%)				
Nonmucinous carcinoma	21 (33.3)	10 (83.3)	10.392	**0.001***
Mucinous carcinoma	42 (66.7)	2 (16.7)		
Grade of the primary tumor *n* (%)				
Grade I	0	2 (16.7)		
Grade II	11 (17.5%)	8 (66.7)	26.209	<**0.001***
Grade III	52 (82.5)	2 (16.7)		
Associated overlying adenoma *n* (%)				
Negative	38 (60.3)	3 (25.0)	5.073	**0.024***
Positive	25 (39.7)	9 (75.0)		
Depth of invasion (T) *n* (%)				
T1/T2	2 (3.2)	2 (16.7)	3.634	0.057
T3/T4	61 (96.8)	10 (83.3)		
Lymph nodes staging (N) *n* (%)				
N1	27 (42.9)	7 (58.3)	0.974	0.324
N2	36 (57.1)	5 (41.7)		

**P* value less than or equal to 0.05 is significant.

Table 5 Characteristics of androgen receptors expression in 75 lymph nodes metastases

	AR expression			
	Negative	Positive	Chi-square (χ^2)	*P* value
Age *n* (%)				
<40 years	20 (30.3)	1 (11.1)	1.447	0.229
>40 years	46 (69.7)	8 (88.9)		
Sex *n* (%)				
Male	43 (65.1)	7 (77.7)	0.568	0.451
Female	23 (34.9)	2 (22.3)		
Histological type *n* (%)				
Nonmucinous carcinoma	23 (34.8)	8 (88.9)	9.538	**0.002***
Mucinous carcinoma	43 (65.2)	1 (11.1)		
Grade of the primary tumor				
Grade I	1 (1.5)	1 (11.1)		
Grade II	15 (22.7)	4 (44.4)	5.288	0.071
Grade III	50 (75.8)	4 (44.4)		
Associated overlying adenoma *n* (%)				
Negative	37 (56.1)	4 (44.4)	0.431	0.511
Positive	29 (43.9)	5 (55.6)		
Depth of invasion (T) *n* (%)				
T1/T2	4 (6.1)	0	0.576	0.448
T3/T4	62 (93.9)	9 (100.0)		
Lymph nodes staging (N) *n* (%)				
N1	30 (45.5)	4 (44.4)	0.003	0.954
N2	36 (54.5)	5 (55.6)		

**P* value less than or equal to 0.05 is significant.

overall survival (OS) are listed in Table 6. The median OS was significantly higher for patients with conventional nonmucinous histology than those with mucinous histology ($P<0.001$). Increasing grade and stage of the tumor were associated significantly with decreasing median OS ($P=0.037$ and <0.001, respectively).

To clarify the prognostic impact of AR expression on survival of CRC patients with LN metastases, a Log-rank test was carried out to compare overall and disease-free survival (DFS) of patients with different AR status in primary tumors and LN metastases. Detailed univariate analyses of the relation of AR expression to survival are listed in Table 7. OS and DFS were not significantly different in cases with negative AR in primaries and LN metastases, cases with positive AR in both, cases with positive AR in primaries only, and cases with positive AR in LN metastases only. Although the median OS and DFS of cases with positive AR expression in either primary carcinomas or LN metastases were much higher than that of cases with negative expression in both primary carcinoma and LN metastases (53 months vs. 22 months and 53 months vs. 19 months, respectively); imparting a good prognostic impact of AR expression;

Table 6 Univariate analysis of prognostic factors in patients with colorectal carcinoma and lymph nodes metastases with respect to overall survival

	Median overall survival (months)	95% confidence interval	Log Rank (Mantel-Cox)	*P* value
Histological type				
Nonmucinous carcinoma	53	40.495–52.860	19.379	<**0.001***
Mucinous carcinoma	18	18.207–26.702		
Grade of the primary tumor				
Grade I	61	58.600–68.400		
Grade II	43	35.998–50.739	s	**0.037***
Grade III	21	22.507–32.456		
TNM staging				
Stage II	61	61.000–61.000		
Stage III	26	28.973–37.970	78.829	<**0.001***
Stage IV	6	4.228–11.272		

**P* value less than or equal to 0.05 is significant.

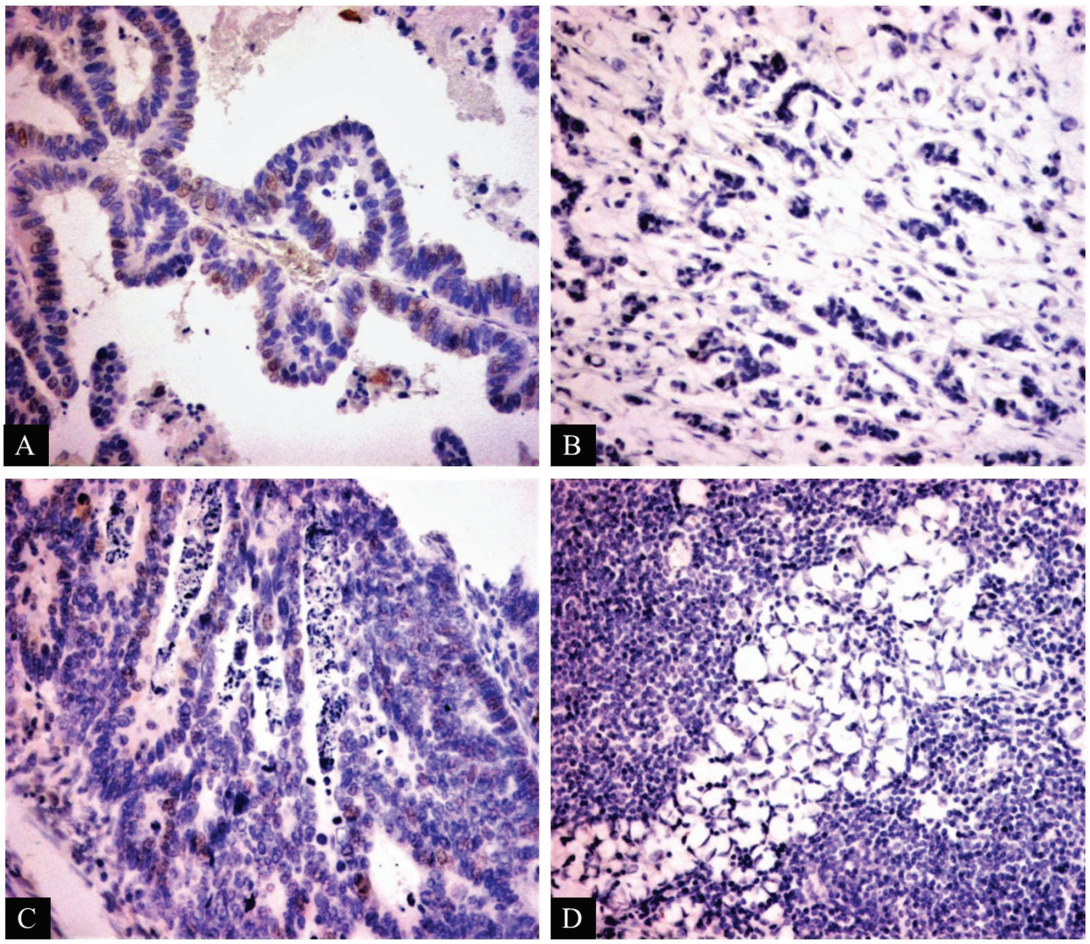
Table 7 Relation of androgen receptors expression with overall survival and disease-free survival in cases with colorectal carcinoma and lymph nodes metastases

	Median overall survival (months)	*P* value	Median disease-free survival (months)	*P* value
Androgen receptors expression in all cases (N=75)				
Negative both carc. and LN (N=60)	22		19	
Positive both carc. and LN (N=6)	28	0.317	28	0.361
Positive carc. and negative LN (N=6)	53		53	
Positive LN and negative carc. (N=3)	58		58	
Androgen receptors expression in all cases (N=75)				
Negative both carc. and LN (N=60)	22	0.064	19	0.081
Positive either carc. or LN (N=15)	53		53	

this was not also statistically significant (P=0.064 and 0.081, respectively) (Fig. 2).

In the cases under investigation, we found that the expression of AR was substantially correlated with some good prognostic clinical and histopathological variables as old age (P=0.018), conventional non-mucinous histology (P=0.001), lower grade (P<0.001), arousal on top of adenoma (P=0.024) and less level of invasion. However, this association was not statistically significant (P=0.057). Huang and colleagues [19] also reported strong correlations between AR expression, larger tumor diameter (P=0.001), and tumor grade (P=0.001) but not age. In contrast, Albasri and Elkablawy [20] reported that AR expression is a poor predictor of CRC, and the tumor's aggressive behavior and the possibility of metastasis are both increased by the presence of AR.

Figure 2



Relation of androgen receptors expression with overall survival and disease-free survival in cases with colorectal carcinoma and lymph nodes metastases; A: Relation of overall survival to androgen receptors status in both primary tumors and metastases. B: Relation of disease-free survival to androgen receptors status in both primary tumors and metastases. C: Relation of overall survival to androgen receptors positivity in either primary or metastatic tumors. D: Relation of disease-free survival to androgen receptors positivity in either primary or metastatic tumors.

Our results also denoted that neoplastic tissues in males showed slightly more AR expression than those in females (58.3% vs. 41.7%, respectively). Statistically, there was no relation between gender and AR status in CRC cases (P=0.504), which was consistent with previous studies [19,20,22]

In addition to these prognostically good factors, our study showed that AR expression is associated with better survival in CRC patients. Even though not statistically significant, cases with positive AR expression had median OS and DFS rates significantly higher than those with negative expression in both primary carcinomas and LN metastases. This is in line with Huang and colleagues [19], who reported that decreased 5-year OS rates for CRC were associated with negative AR expression. Hence, Refaat and colleagues [22] supported the hypothesis that the protein expression of sex steroid receptors like AR in cancerous tissues may serve as prognostic markers, and hormone therapy may offer an alternative method of treating CRC. They reported that the effectiveness of these treatments may vary depending on the patient's gender, clinical stage, and tumor site. Depending on our results, additional factors, such as the patient's age, grade, histological type, depth of invasion, and arousal on top of adenoma, could also affect the effectiveness of these treatments.

In contrast to Shore and colleagues [23], who suggested that male sex steroids may contribute to the development or progression of cancer, our findings are typically in harmony with Roshan and colleagues [24], who reported that sex hormones can offer protection from CRC through the activation of the recently found membrane Androgen Receptor (mARs). These are a group of G protein-coupled receptors that bind and are activated by testosterone and/or other androgens. The activation of these receptors results in the activation of apoptotic pathways that protect CRC. In line with these findings, a previous study also revealed an association between a higher risk of CRC and long-term androgen deprivation therapy for prostate cancer [25].

Another theory was raised by Slattery and colleagues [26] through their Genotyping study, hypothesizing that AR modifies the risk of CRC by working in tandem with substances associated with vitamin D. Furthermore, a cohort study by Xia and colleagues [27] examined the impact of AR methylation levels on the prognosis of CRC and demonstrated that AR hypomethylation is linked to a high risk of CRC.

Conclusion

From our research, we assume that androgen receptors' expression in colorectal carcinoma has a positive predictive influence. To address the prognostic and therapeutic significance of sex steroid hormones and their receptors in colorectal carcinoma patients, additional in vivo and in vitro research is still required. These studies should include larger sample sizes and molecular and genetic studies.

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Availability of data and material

The dataset generated in the current study is available from the corresponding author on demand.

Authors' contribution

All authors read and approved the manuscript.

Research conception and design: AAMF, RMS, MEN, and WME; experiments: AAMF, RMS, MEN, and ETE; statistical analysis of the data: AAMF, HIS, and WME; interpretation of the data: AAMF, HIS, RMS, and ETE; writing of the manuscript: AAMF, HIS, and RMS; work revision and final approval: AAMF, HIS, RMS, WME, MEN, and ETE.

Ethical Approval

The study was approved by the members of the Medical Research Ethics Committee, Institutional Review Board (IRB), Faculty of Medicine, Mansura University, Mansura, Egypt, with Code No.: R.23.08.2303.

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Conflicts of interest

The authors declare that they have no conflict of interest.

References

1 De S, Paul S, Manna A, *et al.* Phenolic phytochemicals for prevention and treatment of colorectal cancer: a critical evaluation of in vivo studies. Cancers (Basel) 2023; 15:993.

2 European Society for Paediatric Nephrology. Twelfth annual meeting, 17–22 September 1978. Arch Dis Child 1979; 54:320–325.

3 Makhlouf NA, Abdel-Gawad M, Mahros AM, *et al.* Colorectal cancer in Arab world: A systematic review. World J Gastrointest Oncol 2021; 13:1791–1798.

4 Sung H, Ferlay J, Siegel RL, *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021; 71:209–249.

5 Foda AA, El-Hawary AK, Hamed H. Aberrant Expression of Calretinin, D2-40 and mesothelin in mucinous and non-mucinous colorectal carcinomas and relation to clinicopathological features and prognosis. Pathol Oncol Res 2016; 22:725–732.

6 Foda AAM, Aziz AA, Mohamed MA. Colorectal signet ring cell carcinoma: Influence of EGFR, E-cadherin and MMP-13 expression on clinicopathological features and prognosis. Ann Diagn Pathol 2018; 32: 41–46.

7 Zalata KR, Elshal MF, Foda AA, Shoma A. Genetic dissimilarity between primary colorectal carcinomas and their lymph node metastases: ploidy, p53, bcl-2, and c-myc expression-a pilot study. Tumour Biol 2015; 36:6579–6584.

8 Kane WJ, Fleming MA2nd, Lynch KT, Friel CM, Williams MD, Hedrick TL, *et al.* Associations of Race, Ethnicity, and Social Determinants of Health With Colorectal Cancer Screening. Dis Colon Rectum 2023; 66:1223–1233.

9 Rehfeld JF. Gastrointestinal hormone research – with a Scandinavian annotation. Scand J Gastroenterol 2015; 50:668–679.

10 Messner EA, Steele TM, Tsamouri MM, *et al.* The Androgen Receptor in prostate cancer: effect of structure, ligands and spliced variants on therapy. Biomedicines 2020; 8:422.

11 Nikolaou S, Qiu S, Fiorentino F, Rasheed S, Tekkis P, Kontovounisios C. The prognostic and therapeutic role of hormones in colorectal cancer: a review. Mol Biol Rep 2019; 46:1477–1486.

12 Kolyvas EA, Caldas C, Kelly K, Ahmad SS. Androgen receptor function and targeted therapeutics across breast cancer subtypes. Breast Cancer Res 2022; 24:79.

13 Nagtegaal ID, Odze RD, Klimstra D, *et al.* The 2019 WHO classification of tumours of the digestive system. Histopathology 2020; 76:182–188.

14 Foda AA. No-cost manual method for preparation of tissue microarrays having high quality comparable to semiautomated methods. Appl Immunohistochem Mol Morphol 2013; 21:271–274.

15 Gasparini P, Fassan M, Cascione L, *et al.* Androgen receptor status is a prognostic marker in non-basal triple negative breast cancers and determines novel therapeutic options. PLoS One 2014; 9:e88525.

16 Janani B, Vijayakumar M, Priya K, *et al.* EGFR-Based Targeted Therapy for Colorectal Cancer-Promises and Challenges. Vaccines (Basel) 2022; 10:499.

17 Gulbake A, Jain A, Jain A, Jain A, Jain SK. Insight to drug delivery aspects for colorectal cancer. World J Gastroenterol 2016; 22:582–599.

18 Brentani MM, Liberato MH, Macedo TM, Habr-Gama A, Laudanna AA. Steroid receptors in Brazilian patients with large bowel cancer. Braz J Med Biol Res 1993; 26:277–284.

19 Uang R, Wang G, Song Y, *et al.* Polymorphic CAG Repeat and Protein Expression of Androgen Receptor Gene in Colorectal Cancer. Mol Cancer Ther 2015; 14:1066–1074.

20 Albasri AM, Elkablawy MA. Clinicopathological and prognostic significance of androgen receptor overexpression in colorectal cancer. Experience from Al-Madinah Al-Munawarah, Saudi Arabia. Saudi Med J 2019; 40:893–900.

21 Wenxuan L, Liu L, Zhang L, Qiu Z, Wu Z, Deng W. Role of gonadally synthesized steroid hormones in the colorectal cancer microenvironment. Front Oncol 2023; 13:1323826.

22 Refaat B, Aslam A, Idris S, *et al.* Profiling estrogen, progesterone, and androgen receptors in colorectal cancer in relation to gender, menopausal status, clinical stage, and tumour sidedness. Front Endocrinol (Lausanne) 2023; 14:1187259.

23 Shore R, Zhang J, Ye W, Stattin P, Lindblad M. Risk of colorectal adenocarcinoma in men receiving androgen deprivation therapy for prostate cancer; a nationwide cohort study. Cancer Causes Control 2023; 34:949–961.

24 Roshan MH, Tambo A, Pace NP. The role of testosterone in colorectal carcinoma: pathomechanisms and open questions. EPMA J 2016; 7:22.

25 Gillessen S, Templeton A, Marra G, Kuo YF, Valtorta E, Shahinian VB. Risk of colorectal cancer in men on long-term androgen deprivation therapy for prostate cancer. J Natl Cancer Inst 2010; 102:1760–1770.

26 Slattery ML, Sweeney C, Murtaugh M, *et al.* Associations between vitamin D, vitamin D receptor gene and the androgen receptor gene with colon and rectal cancer. Int J Cancer 2006; 118:3140–3146.

27 Xia T, Sun H, Huang H, *et al.* Androgen receptor gene methylation related to colorectal cancer risk. Endocr Connect 2019; 8:979–987.