Predictive factor of recurrence after curative resection for stage I-II colon cancer

Facteurs prédictifs de récidive après résection curative pour cancer du colon stade I-II.

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RÉSUMÉ

Introduction: Le cancer du côlon est devenu une pathologie fréquente en Tunisie. Le taux de récidive chez les patients avec un statut ganglionnaire négatif est de 21,1%. Peu d'études ont rapporté les facteurs pronostiques de récidive chez les patients atteints d'un cancer du côlon de stade I-II.
Objectif : Déterminer les facteurs prédictifs de récidive chez les patients atteints d'un cancer du côlon de stade I-II après résection curative.
Méthodes: Il s'agissait d'une étude de cohorte rétrospective. Ont été inclus les patients qui ont subi une chirurgie curative pour un cancer du côlon stade I ou II. Les variables étudiées ont été subdivisées en: variables préopératoires, peropératoires et postopératoires. Le critère de jugement principal était la survenue d'une récidive locale et à distance au cours du suivi.
Résultats: Dix-huit hommes et 17 femmes d'âge médian de 61 ans, allant de 33 à 89 ans, ont été inclus dans l'étude. Vingt-huit patients avaient une tumeur classée T3 et T4. Le nombre moyen de ganglions lymphatiques récoltés était de 16,23 (médiane = 17, [4-44]). Dix patients (28%) avaient une composante colloïde muqueuse au sein de la tumeur. La durée de suivi médiane était de 23 mois (extrêmes: 6-56 mois). Une récidive a été observée dans cinq cas (14%). Les variables associées à la récidive étaient
le taux d'antigène carcino-embryonnaire (p = 0,03), le taux d'albumine sérique (p = 0,029) et la présence de composante colloïde (0,02). L'analyse multivariée a permis de retenir la composante colloïde-muqueuse comme seul facteur prédictif de récidive (OR = 1,2, IC à 95% [1,019-1,412], p =0,028).
Conclusions: Cette étude a montré que le pourcentage de composante colloïde-muqueuse égal ou supérieur à 25% était le seul facteur prédictif de récidive, après résection curative, pour cancer du côlon stades I et II.

Mots-clés
Cancer du colon, StadeI-II, Facteurs prédictifs, Récidive

SUMMARY

Background: Colon cancer has become a common malignant neoplasm in Tunisia. Patients with negative lymph node have a 5 years recurrence rate of 21.1%. Studies reporting the prognostic factors of recurrence for patients with stage I-II colon cancer are limited.
Aim: This study aimed to determine factors predicting recurrence for patients with stage I-II colon cancer after curative resection.
Methods: This was a retrospective cohort study. Were included patients who underwent curative surgery for stage I or II colon cancer. Enrolled variables were subdivided into: Pre-operative, Intraoperative and Post-operative variables. Main outcome measures were local recurrence and distant metastasis detected during follow-up.
Results: Eighteen men and 17 women with median age of 61 years, ranging from 33 to 89, were enrolled in this study. Twenty-eight patients out of 35 were classified T3 and T4 colon cancer. The mean number of lymph nodes harvested was 16.23 (median= 17; range: 4-44). Ten patients (28%) had colloid component in the tumor. At a median follow-up of 23 months (range: 6-56 months), recurrence was observed in five cases (14%). Variables associated to recurrence were Carcinoembryonic antigen level (p= 0.03), serum albumin level (p=0.029) and the presence of colloid component (0.02). Multivariate logistic regression retained colloid component as the only predictive factor of recurrence (OR=1.2, 95%CI [1.019-1.412], p=0.028).
Conclusions: This study showed that the percentage of mucinous component equal or greater than 25% was the only predictive factor of recurrence for curatively resected, stages I and II, colon cancer.

Key-words

INTRODUCTION

Colon cancer has become a common malignant neoplasm in Tunisia [1]. Its incidence is 7 per 100.000 inhabitants per year [1]. Surgery, associated or not to adjuvant chemotherapy, is the cornerstone of the management. Patients with lymph node metastasis have a significantly shorter disease free survival (DFS) when compared to those having a negative lymph node status [2]. Furthermore, patients with negative lymph node have a 5 years recurrence rate of 21.14% [3]. Studies reporting the prognostic factors of recurrence for patients with stage I-II colon cancer are limited [2-9].

This study aimed to determine factors predicting recurrence for patients with stage I-II colon cancer after curative resection.

METHODS

It's a retrospective study enrolling consecutive patients between January 1st, 2008 and December 31st, 2012.

Eligibility criteria:

Were included patients who underwent curative surgery for stage I or II complicated and non-complicated colon cancer. The 7th edition American Joint Committee of Cancer (AJCC) staging manual classifies stage I tumors as T1 (submucosa) and T2 (muscularis propria) and it classifies stage II tumors as T3 (subserosa or beyond) and T4 (adjacent organs), without lymph nodes invasion or distal metastasis [4].

Non eligibility criteria:

All patients under the age of 18, those who had positive lymph node or distant metastasis, patients with R1 or R2 resection and patients who deceased during post-operative course, were not included.

Design:

Enrolled variables were subdivided into:

*Pre-operative variables which included: 1) Age, 2) Sex, 3) Comorbidities 4) American Society of Anesthesiologists Physical Status Classification System (ASA score) [10], 5) Diagnosis delay, 6) Clinical variables, 7) Endoscopic variables, 8) Invasion of the adjacent organs, 9) Biological variables (Carcino Embryogenic Antigen (CEA), Hemoglobin, Albumin)

*Intraoperative variables which included: 1) Emergency status, 2) Laparoscopic approach, 3) Invasion of the adjacent organs, 4) Tumor perforation, 5) Tumor Abscess, 6) Type of colectomy, 7) Mechanical suture, 8) Tumor size (cm), 9) Polyps number, 10) Pathological examination (Differentiation, Invasion of the adjacent organs, TNM classification, Nerve sheathing, Vascular emboli, Colloid component)

*Post-operative variables which included: 1) Hospital stay, 2) Post-operative course, 3) Medical complications, 4) Surgical complications (peritonitis, anastomotic fistula), 5) Adjuvant chemotherapy (duration, delay between surgery and starting chemotherapy, Number of cures), 6) Follow up (Alive without recurrence, Alive with recurrence, Hepatic metastasis, Pulmonary metastasis, Follow up duration)

Main outcome measures:

Main outcome measures were local recurrence and distant metastasis detected during follow-up. The follow-up process was based on physical examination and CEA test every three months and thoraco-abdominal computed tomography (CT) scan every six months, during the first two years. Colonoscopy was realized one year after surgery. From the third year of follow-up, physical examination and CEA test were performed every six months. Whereas, thoraco-abdominal CT scan and colonoscopy were practiced every year.

Statistical analysis:

Qualitative variables were presented with percentage accompanied by 95% confidence interval. Quantitative variables were presented with mean and standard deviation (SD), whenever variable distribution was normal. Otherwise, it was presented by median with range values. Bivariate analysis comparing recurrence versus DFS groups was performed by X^2 test, Fisher exact test, Student T test and Mann Whitney test when appropriate. Variables associated to $p \leq 0.05$ by bivariate analysis were introduced in logistic regression model to identify independent variables predicting recurrence which were expressed by Odds ratio with 95% confidence interval. $P \leq 0.05$ defined the level of statistical significance. For continuous predictive variables, ROC curve identified the cut-off point with the best couple sensitivity-specificity. Sensitivity, specificity, predictive values and positive likelihood ratio were reported with their respective 95% confidence interval.

RESULTS

Table 1 summarizes the baseline characteristics of patients. Eighteen men and 17 women with median age of 61 years, ranging from 33 to 89, were enrolled in this study. Thirty one percent of patients had cardio-vascular disease. Colon cancer was revealed by complications in 23% of cases. Eighty nine percent of tumors were adenocarcinoma. The tumors were localized in the sigmoid (49%), in the right colon (26%), in the descendant colon (14%) and the recto sigmoid junction (11%). Fifty one percent had stenosis tumor.

Seven patients had laparoscopic approach and 28 had open approach. Twenty eight patients out of 35 were classified T3 and T4 colon cancer. The mean number of lymph nodes harvested was 16.23 (median= 17; range: 4-44). Eight patients (22%) had less than 12 retrieved lymph nodes. Seven patients (20%) had perineural invasion and four patients (11) had lymphovascular invasion. Ten patients (28%) had colloid component in the tumor. At a median follow-up of 23 months (range: 6-56 months), recurrence was observed in five cases (14%). Regarding recurrence, three patients had a liver metastasis, one had a local recurrence and one had lung metastasis.

Bivariate analysis showed three variables associated to recurrence: Carcinoembryonic antigen (CEA) level (p= 0.03), serum albumin level (p=0.02) and the presence of colloid component (0.02) (Table 2). Multivariate logistic regression retained colloid component as the only predictive factor of recurrence (OR=1.2, $^{95\%}$CI [1.019-1.412], p=0.02) (table 3).

ROC curve analysis for the continuous variable colloid component showed an area under curve equal to 0.988, $^{95\%}$CI [0.95-1], p=0.002 (Figure 1). The cutoff point of 25% of colloid component had a sensitivity of 100% ($^{95\%}$IC [100-100]), and a specificity of 97% (CI $^{95\%}$ [91-100]). The positive predictive value and the negative predictive value of this cutoff point were respectively 80% ($^{95\%}$CI [45-100]) and 100% ($^{95\%}$CI [100-100]). Positive likelihood ratio was 31 ($^{95\%}$CI [4.5-213]). Negative likelihood ratio was 0.

Table 1: Baseline characteristics of patients.

Variables		N (%) or median with [IQR] and (range)
Demographic		
	Age	61 [48-72] (33-89)
	Gender (women)	18 (51.4%)
Diabetes		4 (11.4%)
Cardiovascular disease		10 (28.6%)
Renal insufficiency		4 (11.4 %)
Obesity		5 (14.3%)
ASA score		
	I	20 (57.1%)
	II	13 (37.1%)
	III	2 (5.7%)
Diagnosis delay		90 (2-710)
Symptoms and physical exam		
	Occlusion	7 (20%)
Ò‹‹	Constipation	8 (22.9%)
	Diarrhea- constipation	7 (20%)
	Abdominal pain	19 (54.3%)
	Melena / bleeding	7 (20%) / 7 (20%)
	Patients with Weight Loss	13 (37.1%)
	Weight loss	8,5 (2-30)
	Abdominal mass	4 (11.4%)
	Fever	2 (5.7%)
	Revealing complication	8 (23%)
Endoscopic Findings		
	Right colon tumor	9 (31%)
	Left colon tumor	18 (62.1%)
	Circumferential tumor	22 (62.9%)
	Double localization	2 (5.7%)
	Presence of Polyps	8 (22.9%)
	Stenozing tumor	18 (62.1%)
Laboratory findings		
	CEA	3 (0,3-122)
	Hemoglobin	11,7 (6,7-15)
	Albumin	32 (20-37)
Invasion of adjacent organ on CT scan		2 (5.9%)

Intraoperative variables	
Emergency operation	6 (17.1%)
Laparoscopic approach	7 (20%)
Invasion of adjacent organs	5 (14.3%)
Tumor perforation	2 (5.7%)
Tumor Abscess	1 (2.9%)
Total colectomy	2 (11.8%)
Right colectomy	4 (23.5%)
Left colectomy	3 (17.6%)
Mechanical suture	12 (40%)
Tumor size (cm)	4 (2-6)
Pathological examination	
Well differentiated	29 (82.9%)
adenocarcinoma	3 (8.6%)
Invasion of the neighboring	17 (4-44)
organs	1 (2.9%)
Number of Lymph nodes	6 (17.1%)
examined	21 (60%)
T1	7 (20%)
T2	7 (20%)
T3	4 (11.8%)
T4	10 (28.6%)
Nerve sheathing	0 [0-10] (0-55)
Vascular emboli	
Colloid component	
Percentage of colloid	
component (%)	
Post-operative course	
Overall morbidity	6 (17.1%)
Medical complications	3 (8.6%)
Peritonitis	1 (2.9%)
Anastomotic fistula	2 (5.7%)
Hospital stay	9 [7-15] (0-34)
Adjuvant chemotherapy	
Delay of starting chemotherapy after	6 (3-12)
surgery	2 (1-4)
Number of cures	6 (3-12)
Length (months)	
Follow up	23 [16-49] (33-89)
Recurrence	5 (14%)
Hepatic metastasis	3
Pulmonary metastasis	1
Local	1

IQR: inter quartile range

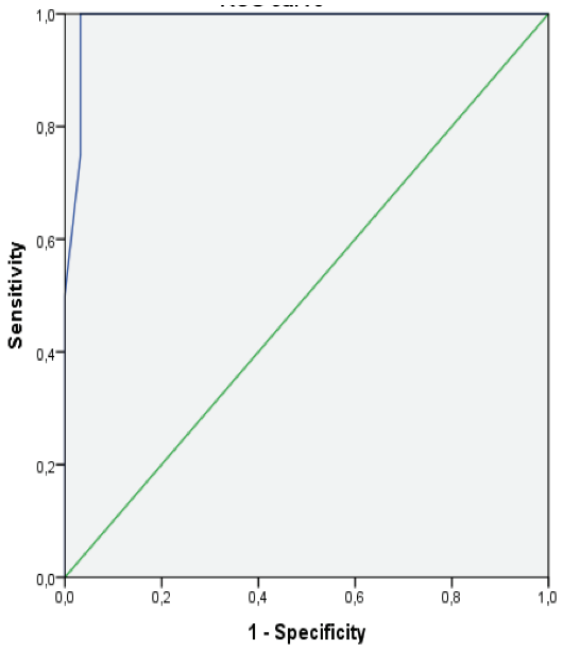

Figure 1: Multivariate analysis: ROC curve

DISCUSSION

This study showed that the percentage of mucinous component equal or greater than 25% was the only predictive factor of recurrence for curatively resected, stages I and II, colon cancer with a sensitivity= 100%, a negative predictive value= 100% and a positive likelihood ratio = 31 ($^{95\%}$CI [4.5-213]).

Current prognosis of colon cancer is based on pTNM classification. However, in terms of tumor relapse risk, other prognostic factors should be considered for each stage.

Verhulst's meta-analysis published in 2012, showed that mucinous differentiation leads to an increase in the risk of death of 2 to 8 [11].

Park *et al* [12] showed that mucinous adenocarcinoma was found at more advanced stage, located mainly at the right side and was an independent factor of survival in colon cancer.

Sadahiro *et al* [5] showed that the prognosis was worse with a colloid component area ratio of 10% or more than with a colloid component area ratio of less than 10% ($P<0.05$).

Table 2: Recurrence, bivariate analysis.

Variables	No recurrence (n= 30)	Recurrence (n=5)	p
Demographics			
Age (mean ± SD)	61.81 ± 15.37	60 ±15.25	0.900
Gender			
Men	17	1	0.338
Women	14	3	
Diagnosis delay	139.83±168.15	191±201.19	0.740
Abdominal mass			
Yes	2	1	0.313
No	29	3	
Revealing complication			
Yes	7	24	1.000
No	1	3	
CEA serum level	4.7±1.52	59.00±31.60	0.003
Hemoglobin	11.59±1.77	11.05±2.60	1.000
Albumin serum level	32.33±3.53	25.5±3.53	0.029
Invasion of adjacent organ on CT scan			
Yes	2	0	1.000
No	28	4	
Intraoperative variables			
Invasion of adjacent organs	3	2	0.890
Tumor perforation	1	0	1.000
Tumor Abscess	1	0	1.000
Tumor size	4.59±1.96	4.25±1.25	0.890
Pathological examination			
Number of Lymph nodes examined	16.1±8.57	19.75±5.31	0.415
T1	1	0	1.000
T2	4	2	0.120
T3	20	1	0.270
T4	5	2	0.540
Nerve sheathing	6	1	1.000
Vascular emboli	4	0	1.000
Colloid component	5	5	<0.001
Percentage of colloid component % (IQR)	0 (0-0) [0-40]	45 (35-52.5) [30-55]	<0.001
Adjuvant chemotherapy			
Yes	13	2	1.000
No	18	2	

Table 3: Predictive factor of recurrence, multivariate analysis

Variables	OR	CI 95%	p
Colloid component %	1.2	[1.019-1.412]	0.028

Besides, Minsky *et al* [6] revealed that colloid component decreased the 5-year survival of patients with colorectal cancer, but the result wasn't statistically significant. However, Halvorsen *et al* [7] didn't consider colloid component as a significant independent prognostic factor unless the major tumor component is represented by signet ring cells. Kim *et al* [8] found that colloid component was an independent factor of poor prognosis for DFS but only in stage III colon cancer after adjuvant chemotherapy. Markl *et al* [9] showed that lymph nodes with diameters larger than 5mm (LN5) number as well as infiltration type were independent prognostic factors. Takahashi *et al* [13] revealed that vessel count and VEGF expression predicted recurrence in patients with negative node colon cancer. Sloothaak *et al* [14] revealed that micro metastases have a worse prognosis than patients without occult tumor cells (OR 5.63; $^{95\%}$CI 2.4 - 13.13). Sinicrop *et al* [15] revealed the association between the body mass index (BMI) and the colon cancer prognosis. In fact, obese patients class 2/3 (BMI ≥35.0 kg/m2) had significantly poorer survival and an increase in cancer recurrence. Moreover, men with class 2/3 obesity had a statistically significant reduction in DFS

[HR= 1.16 (1.01, 1.33), p=0.0297] compared to normal weight patients. Resnick *et al* [16] revealed that lymph vascular invasion (P=0.01) and low levels of claudin-1 expression (0, +1) (P=0.0001) were independent factors of recurrence. Besides, they showed that a loss of claudin-1 expression (P= 0.0001) was associated with poor survival. Cao *et al* [17] identified age, type of surgery, histological subtypes, tumor size, tumor location, lymph nodes metastasis, distant metastasis, Dukes' stage and p53 expression levels, as independent factors that may influence the survival rate of patients with colon cancer following surgery (P<0.05). However, this study considered all patients with colon cancer which differed from our study which analyzed only stage I and II colon cancer. Resnick *et al* [18], in a retrospective study restricted to stage II colon cancer patients who did not undergo adjuvant therapy, showed that p53 (P = 0.04), high level of EGFR (P = 0.05), and lymphovascular invasion (P = 0.03) were independent factors of recurrence. Besides, both of p53 (P = 0.02) and EGFR (P = 0.01) were associated with poor survival. Kenneth *et al* [2] showed that lymph node status was the only significant independent factor predicting cancer-specific survival (hazard ratio: 3.52, $^{95\%}$CI: 1.60–7.71, p = 0.002) and disease-free survival (hazard ratio: 3.42, $^{95\%}$CI: 1.75–6.69, p < 0.001). Pei-Rong Ding *et al* [19] showed that elevated neutrophil to lymphocyte ratio (NLR >4) (hazard ratio, 4.88; P<0.01) and less lymph node sampling (<15 lymph nodes; hazard ratio, 3.80; P<0.05) were adverse prognostic factors for recurrent-free survival (RFS). The 5-year RFS was 91.4% ($^{95\%}$CI, 88.6–94.2%) for patients with normal NLR and 63.8% (51.1–76.3%) for patients with elevated NLR. The 5-year RFS for patients with 0, 1, and 2 of the identified risk factors was 95.1%, 87.4%, and 33.3%, respectively (P<0.001). Mallappa *et al* [20] revealed that preoperative neutrophil to lymphocyte ratio NLR >5 (HR 1.81, $^{95\%}$CI 1.07-3.07, P = 0.028) was an independent risk factor of recurrence. Shingo *et al* [21] considered peritoneal cytology as an

Table 4: Predictive factors of recurrence for colon cancer

Study:	Predictive factors:
Sadahiro [5]	Colloid component area ratio of 10% or more
Bruce [6]	Colloid component
Halvorsen [7]	Colloid component
Kenneth [2]	Lymphovascular invasion
Markl [9]	Lymph nodes with diameters larger than 5mm (LN5)
Verhulst [11]	Mucinous adenocarcinoma
Park [12]	Mucinous adenocarcinoma
Takahashi [13]	Vessel count, VEGF expression
Sloothaak [14]	Micro metastases
Sinicrop [15]	BMI ≥35kg/m2
Resnick [16]	Low levels of Claudin-1 (0,+1) and Lymphovascular invasion
Cao [17]	P53 expression, histological subtypes, Distal Metastasis, Tumor size and location
Resnick [18]	increased EGFR and P53 levels
Pei-Rong Ding [19]	Lymph nodes <15, elevated neutrophil to lymphocyte ratio NLR >4
Mallappa [20]	Preoperative neutrophil to lymphocyte ratio NLR >5
Shingo [21]	Positive peritoneal cytology
Tsai [22]	Vascular invasion, perineural invasion, high postoperative CEA levels
Poincloux [23]	Loss of Bcl-2 expression

independent predictor of cancer specific survival in all patients and in patients with pT3 or pT4 tumors. Only peritoneal cytology was a significant prognostic factor for peritoneal recurrence (P <0.0001) [21]. Tsai *et al* [22] demonstrated that the presence of vascular invasion (P = 0.033), the perineural invasion (P = 0.005), and the high postoperative CEA levels (P = 0.001) were independent factors of postoperative early recurrence. Poincloux *et al* [23] revealed that, among the 59 stage II patients, Bcl-2 was a predictive of relapse-free survival (P=0.025) but not of overall survival (P=0.09).

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