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LA LOCALISATION TUMORALE DES CANCERS DU COLON DROIT NE MODIFIE PAS LA LONGUEUR DE RESECTION COLIQUE : EXPERIENCE DU CHU DE GRENOBLE

THESE
PRESENTEE POUR L'OBTENTION DU DOCTORAT EN MEDECINE

DIPLÔME D'ETAT

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par SIEBERT Matthieu, *[Données à caractère personnel]*

DEVANT LE JURY COMPOSE DE

Président du jury :

M. le Professeur FAUCHERON Jean-Luc, PU-PH

Membres :

M. Le Professeur CHAFFANJON Philippe, PU-PH

M. le Professeur PIOLAT Christian, PU-PH

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Abstract

Background : Colorectal cancer is increasingly recognized as representing a heterogenous group of tumors. While left segmental colectomy is an accepted and oncologicaly safe practice for left-sided colonic cancer (CC), most authors agree that there is no room for effective segmental resection of right-sided cancer for oncological objectives. Length of the resected colon is an important point of debate. To our knowledge, caecum and ascending CC have not been analysed like different groups of tumors. The objective of this study is to see if retrospectively in our center, surgical treatment of caecal cancer would differ with ascending colon cancer.

Methods : A retrospective review of all consecutive patients with right colonic resection for cancer admitted to the University hospital of Grenoble from January 2005 to August 2016 was performed. Main outcome of this study was to compare the length of colonic resection, between caecal primary cancer and ascending colonic cancer.

Results : Among operated patients, tumor was localised preoperatively on caecum in 110 cases and on the right ascending colon in 119 cases. Preoperative localisation had no effect on the colonic length resected (mean 24.5, 24 +/-10.34 vs 25 +/-7.28, p=0.95), on the number of harvested lymph nodes with a mean of 15 (+/- 7.6) nodes in the caecal group versus 15.2 (+/-7.3) (p=0.72). We noticed 15 cases of discordance between pre and post operative location (4 vs 11, p =0.08).

Conclusion : In our center, we have not foud statistical differences in length resection from tumors located on the caecum or in the ascendant colon.

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Background :

Radical surgery for colonic cancer is the only treatment modality for a definitive cure [1] however the management of right colon cancer still lacks international standardization. While left segmental colectomy is an accepted and oncologicaly safe [2] practice for left-sided colonic cancer (CC), most authors agree that there is no room for effective segmental resection of right-sided cancer for oncological objectives [3]. Length of the resected colon is an important point of debate [4]. Japanese scientific societies [5] recommend mucosal margins between 5 and 10 cm according the lymph flow direction, whereas western advice [6] still favours the "dogm" of 5cm-margin on the bowel. But the evidence for "5 cm resection" is weak (rated level IV) [7]. There is still a debate about the interest of extended right hemicolectomy. Extensive mesenteric resection in right-sided colon cancer does not increase overall survival or produce a better oncological result, but increases perioperative morbidity [8,9].

Another important point of debate is extent of the lymphadenectomy. Current Japanese [5] and western recommendations [6] advocate a D2 lymphadenecotmy in most cases, and a D3 lymphadenectomy in cases of pre- or per-operative suspicion of lymphatic metastasis in this drainage territory. Anatomic variations in the distribution of the right-sided colic arteries make it difficult to standardize lymphadenectomy [10]. Some studies show a clear advantage in high ligation [11], whereas others show no demonstrable benefit [12,13]. Some studies have shown similar oncological results with an increase of perioperative morbidity [8,13]. Currently there is clearly no sufficient scientific proof to recommend high ligation, however this does not prevent some authors promoting it for right-sided colonic cancer [10].

Concerning lymphadenectomy, Park et al. [3] retrospectively reviewed the position of lymph node metastasis along the arterial trunks and interestingly found that the distribution of lymphatic metastasis for caecal tumors was 12.2% along the right colonic artery and 6.1% along the right branch of the middle colic artery. Such an important rate should be questioned, indeed the rate of 12.2% of lymphatic metastasis metastasis has to be balanced with the highly variable presence of the right colic artery (RCA) in the literature, ranging from 10% to 63% [14–16], with several authors reporting that a true right colic artery is rarely seen, with approximately 15% prevalence [15,17]. However those results clearly discourage a segmental colectomy like ileocaecal resection which could lead to insufficient lymphadenectomy.

Despite these findings countering extensive resection, the current trend in the literature is to adopt the complete mesocolic excision (CME) with central vascular ligation (CVL). The concept is to use the

analogy of TME to extend this practice to colonic resection. This technic incorporates three concepts [18]. Ligation of the mesenteric vessels near the origin, facilates a D3 lymphadenectomy [19,20] and large extensive bowel resection [19] with proximal and distal mucosal margins of 10 cm [21]. They also insist on a third point, « en block » resection, with dissection conducted between the embryological planes. This technic is not yet recommended despite encouraging anatomopathological and clinical results [17,22–26]. However, to our knowledge prospective, comparative multicentric studies which can lead to its generalization do not exist. The current studies comparing CME with « standard » surgery [22,23] accumulate a lot of bias [27]. The first study [22] did not report any clinical data, the only difference was the rate of harvested nodes; while the other [23] found clinical benefits in retrospectively comparing outcomes coming from differents centers, which is an inherent source of bias.

Most authors agree, that the number of lymph nodes harvested (NLNH) is closely related to the prognosis of CRC, and increased NLNH is significantly associated with decreased risk of disease recurrence and death [28–34]. Likewise, with patients undergoing right hemicolectomy, the length of resected ileum does not influence local recurrence rates [6]. It also has been shown that a dissection along the planes, between parietal and visceral superior is pathologically and clinically superior when comparing it with an incomplete or partly torn specimen [22,24,35].

In order to be as clear as possible, in this study, we used the following definitions : A right hemicolectomy is defined as removal of the terminal ileum and the ascending right colon followed by an ileo-transverse anastomosis [36]. Extended right hemicolectomy refers to extension of the distal resection margin to include the distal transverse colon up to the splenic flexure. We used the most widely accepted definition of the caecum : the colon under the superior edge of the ileocaecal valve, with the ileocecal valve being included in the caecum [37]. Most authors agree that right hemicolectomy is indicated in patients with cancer of the right colon, caecum to the right segment of the transverse colon. Mesocolon excision must include the ileocolic artery, the right colic artery and the right branch of the middle colic artery [38]. Most authors recommendations agree that an adequate lymph node evaluation needs to gather at least 12 lymph nodes [39].

Colorectal cancer is increasingly recognized as representing a heterogenous group of tumors [40], wich is why an analysis on the basis of tumor location is essential. To our knowledge, caecum and ascending CC have not been analysed like different groups of tumors. Their characterisation could be a first step leading to segmental resection in right-sided colonic cancer.

The objective of this study is to see if retrospectively in our center, surgical treatment of caecal cancer would differ with ascending colon cancer.

Methods :

Data sources

A retrospective review of all consecutive patients with right colonic resection for cancer admitted to the University hospital of Grenoble from January 2005 to August 2016 was performed. Patients were identified using the medical information department.

We excluded patients with factor who could impact the length of colon resection : Patients with Chron's disease, colorectal cancer antecedent, synchronous colorectal tumors, nonepithelial malignancies (lymphoma or carcinoid, appendical neoplasms...), peritoneal carcinomatosis, generalized peritonis and occlusion resistant to a medical treatment, pediatric patients (aged less than 18).

Demographics

Patient demographics, including age at diagnosis, gender, signs and symptoms present at the first medical examination were collected. Signs and symptoms involved in CRC were classified as follows : associated with bleeding or anemia (melena, posive fecal occult blood and anemia ; associated with passage trouble (ileus, abdominal pain, altered bowel habit, abdominal distension and vomitus), abdominal mass, and others (e.g. general fatigue, fever, weight loss)

Population

Among the 294 patients who underwent right colonic resection for cancer in our center, 3 patients had a history of inflammatory bowel disease, 4 had synchronous colorectal disease or colorectal antecedent. 22 patients with colic tumor other than adenocarcinoma were excluded. 4 patients diagnosed with peritoneal carcinomatosis were also excluded. Characteristics of the 22 patients with right transverse colonic tumors were not analysed.

To establish the localisation of the tumor, abdominal tomodensitometry and colonoscopy were used : To assess preoperative location, colonoscopy was prefered to CT-scan. CT scan was used to define the preoperative location in the case of absence of preoperative colonoscopy or in case of incomplete colonoscopy, all tumors astride the ileo-colic valvula were included in the caecum group. Definitive location of the tumor was defined conforming to the anatomopathological piece.

Technical details

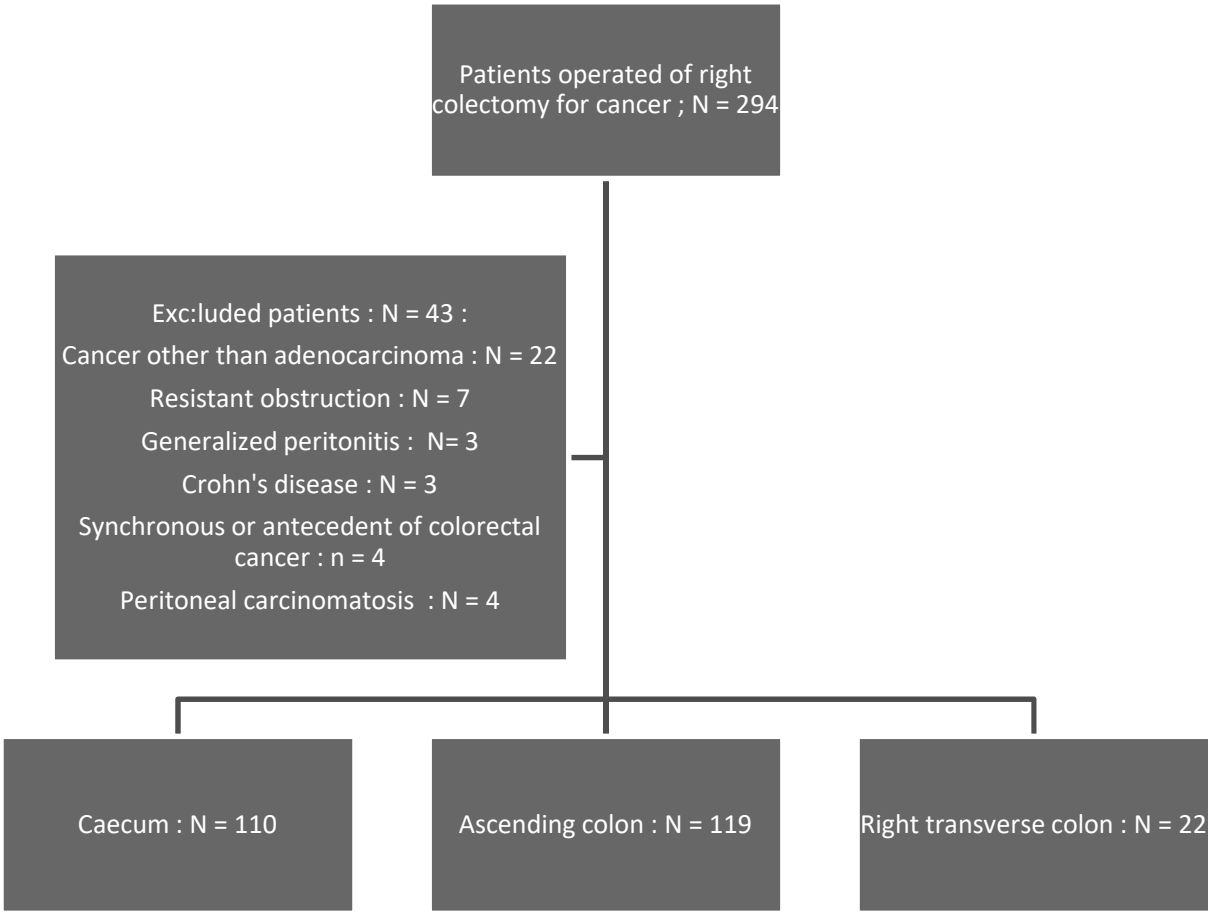
CME with CVL as it is described by Hohenberger [24] is not currently practiced in our center. The most current technic used in our center could be described as « standard » right hemicolectomy, with ileo-colic anastomosis and D2 type lymphadenectomy.

Other data :

Anatomopathologic grades, TNM (American Joint comittee on cancer 2009), size of the tumor, imaging information, BMI, as well as therapeutic interventions and hospital disposition were extracted prospectively and comprehensively recorded from the classic and the computerized medical record.

Clinical data, such as survival or relapse aswell as histopathological data, such as intact mesocolon or distal margins was not recorded.

Table 1 : Population



Main outcome of this study was to compare the length of colonic resection, between caecal primary cancer and ascending colonic cancer.

Number of lymph nodes gathered, TNM stage, pT stage, pN stage, demographics, diameter of the tumor, discordance between preoperative and postoperative location and preresection status (non metastatic, carcinosis, metastasis), laparoscopic versus open resection were also analysed.

Categorical data was compared using the chi-squared test. Continuous data was compared using the independent sample Student's T test.

Results :

Profiles of enrolled patients, discovery circumstances, surgical approach and staging of the disease are sum-marized in Table 2.

The mean age of patients was 74 years, and 52.4 % (n = 120) of patients were male. Among operated patients, tumor was localised preoperatively on caecum in 110 cases and on the right ascending colonin 119 cases. The two groups were comparable in terms of gender, BMI, discovery circumstances and surgical approach. Patients affected with caecal tumors were older than those with ascending colonic cancer (77 +/- 11.28 vs 74 +/-10.70, p=0.01), were suffering more advanced disease (p = 0.035), with larger tumors (5.5 +/-2.47 vs 4.5 +/- 2,59; <0.01).

Preoperative localisation had no effect on the colonic length resected (mean 24.5, 24 +/-10.34 vs 25 +/-7.28) (Table 3) on the number of harvested lymph nodes with a mean of 15 (+/- 7.6) nodes in the caecal group versus 15.2 (+/-7.3) (p=0.72).

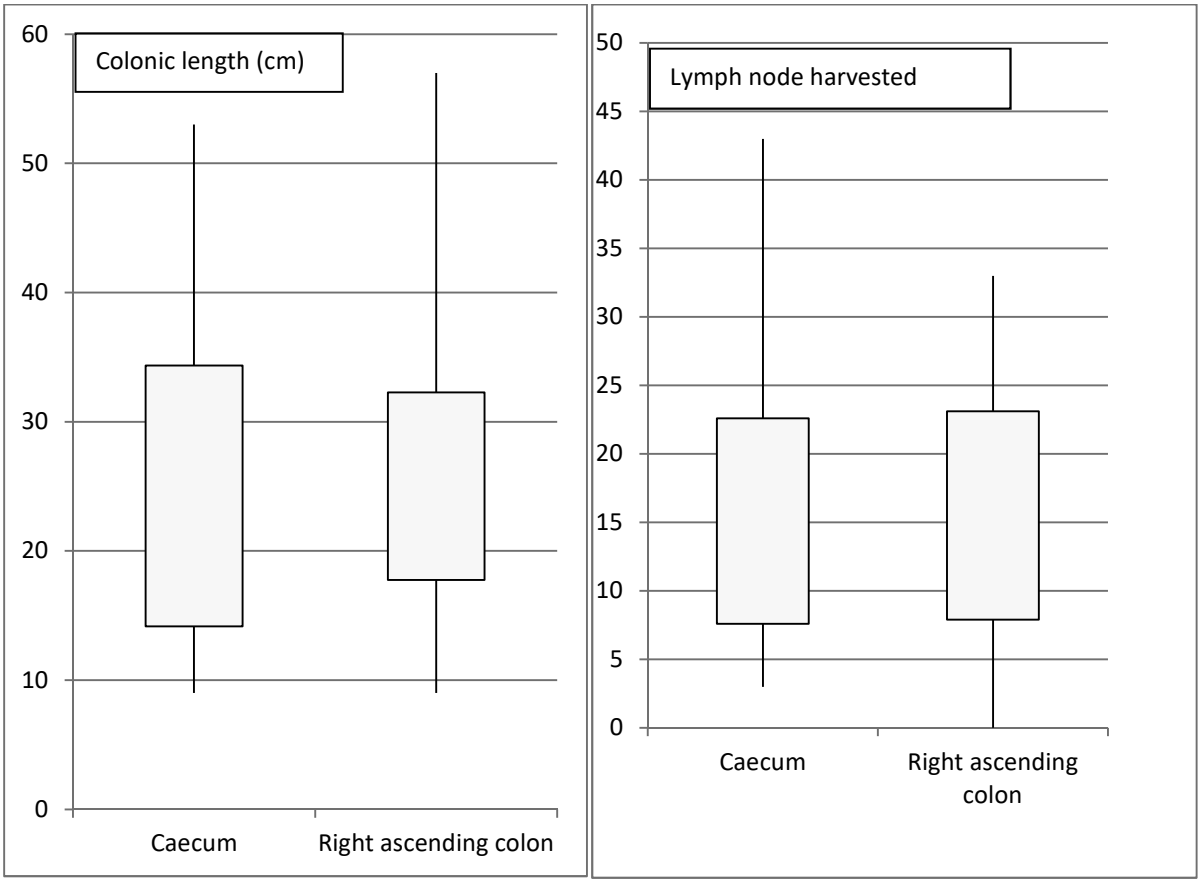
74% (N = 170) of all patients received adequate lymph node evaluation, and there was no statistical difference between the two groups.

We noticed 15 cases of discordance between pre and post operative location (4 vs 11, p =0.08), with statistical difference.

Table 2 : Population, results

	Total N = 229	Caecum N = 110	Right ascending colon N = 119	P
Sex				0.198
Male	120	63	57	
Female	109	47	62	
Age	74	77	73	**0.0118**
Discovery circumstances				Comparison impossible
Associated bleeding or anemia	111	47	64	
Passage trouble	52	31	21	
Abdominal mass	4	4	0	
Others (AEG, fever, weight loss)	22	14	8	
No symptomas	40	14	26	
BMI median	24,74	24,69	24,98	0.1772
Surgery				Comparison impossible
Right hemicolectomy	225	106	119	
Ileocaecal resection	4	4	0	
Surgical approach				0.2641
Laparotomy	135	69	66	
Laparoscopy	85	33	52	
Converted laparoscopy	9	8	1	
Colonic length resected (median)	24.5	24	25	0.9517
Nb of lymph nodes harvested (median)	15	15	15.2	0.7211
Adequate lymph nodes evaluation	170 (74%)	81 (73.6%)	89 (74.7%)	0.9194
Discordance Pre/post surgery	15	4	11	0.086619
Tumor diameter	5	5,5	4,5	**<0.001**
Stage TNm				**0.0357**
I	47	14	33	
II	86	48	38	
III	71	35	36	
IV	25	13	12	

Table 3 : Colonic length and number of lymph node harvested regarding to the tumor location



Discussion

The first consequence we can get from this study that there is apparently no variations of the length of colonic resection whether the tumor is located on the caecum or the right ascending colon in our center. Retropectively, this data suggests that the type of colonic resection is the same, whether the tumor is located on the caecum or on the ascendant colon. This is in agreement with the previous descriptions of right colonic resection in the western world.

Study	Year	CME with CVL	Lymphadenectomy	Lenght of colon	NLNH	Adequate lymph node evaluation (%)	Tumor size
Siebert and al	2016	No	D2	24.5	15	74	5
Subbiah and al [25]	2016	Yes	D3	34	24	97	5
West and al, [4] *Erlangen*	2012	Yes	D3	25.1	32	n.c.	n.c.
West and al, [4] *Tokio*	2012	No	D3	16.8	24	n.c.	n.c.
West and al, [22] *Leeds*	2009	No	D2	18.3	16	n.c.	n.c.

Table 4 : Comparison with the results in the literature

The data provided in this study show comparable results with the D2 and non-CME techniques, but inferior compared to the technique using CME or D3 lymphadenectomy.

It is accepted that NLNH is a very important factor for prognosis in colonic surgery, but its significance should be interpreted with caution. Indeed, the NLNH has many confounding factors and many potentials sources of bias are identified in the literature : demographic variables such as age[26,34], geographic location [41–43] (17), BMI [43], surgery-related factors, such as experience and case volume [44,45], level of resection of the supplying artery, segments of bowel, location of the tumor [29,42] or even disease related factors such as tumor size, higher T stage (3) [34]. Pathologist-related factors or pathology technique used can also influence results [46,47].

Only two studies comparing [22,23] CME versus “standard” hemicolectomy fail to described what is “standard” colectomy and compare different centers, sometimes between differents countries [22].

One major criticism of these studies is that those confounding factors that entails could contribuate to these results.

It's not surprising in the light of the description of the technique that this procedure tends to remove a longer length of colon in right-sided colonic cancer, and leads to a greater lymph node yield [4,22,24]. But oncological outcomes are very controversials, and any possible benefit to survival is still unproven [2,13,27,48–50]. But CME benefits remain untested in comparative prospective trials and more importantly, some advocate that routine implementation of CME carries the risk of patient harm due to longer operating times, vascular damage and autonomous nerve damage [27]. Furthermore, large mucosal margins do not seem to be mandatory because Japanese D3 resection, with more limited bowel resection, has shown similar results to CME surgery [4,51,52].

These findings on the increased NLNH with the CME procedure lead some authors to discuss its benefit to survival [27], and argue that observed relationship between nodal counts and outcome in CC is most probably not causal but a confounded factor. Indeed local recurrences potentially prevented by CME are very rare events compared to rectal cancer [53], are not caused by less extensive resection [54,55], and as it has been described in earlier comparative studies, have failed to demonstrate any survival benefit associated with extensive, additional or extra-mesenteric lymphadenectomy.

In our opinion, CME should not be interpretated as an original technique, because it is just a combination of 3 components among which only one (« along the plane dissection ») shows clear scientific benefit, while there is no benefit demonstrated fot the two others. Some propose that « en block resection » is only a marker of good practice, wich has not been introduced by the concept of CME [27,56]. In deed, a recent meta-analysis demonstrated that performing a high arterial ligation in CC does not improve overall survival [57]. Together, this data fails to demonstrate that extensive surgery improves survival in CC, which argues against a surgical therapeutic effect as an explanation of the observed relationship between NLNH and survival.

Right colonic cancers are frequently described as poorer pronognis cancers because of higher TNM-stage, larger tumors, increased frequency of vascular invasion, mucinous type, high grade and invasive tumor border compared to left colorectal caner (LCRC) [58–61]. That could be an explanation why historically surgeons have excluded the option of the segmental resection. However, the recent mass screening generalization could lead to an earlier diagnosis with less advanced tumors.

In colorectal surgery, segmental resection needs a precise preoperative assesment. In deed, the preoperative localisation has to be reliable. The necessity is even more important because of the trend toward laparoscopic resection. Our results are comparable with existenting literature.

Colonoscopy is the most accurate and versatile diagnostic test for CC [62]. Witch localisation error described from 4.0 to 20.8 %in the literature [62–64]. It should be noted that preoperative tatooig has been described as a technique who could improve preoperative localisation accuracy [65–68]. Its impact on and benefit in relation to LN retrieval and CRC staging is controversial [69–75].

Diagnostic colonoscopies performed by an operating surgeon rather than a non operative colonoscopist are independently associated with a lower localization error rate [62].

This study does present some weaknesses : it is a retrospective, monocentric, historic study with eldery patients which can explain the large part of laparotomy's resection. Although we attempted to account for cofounding factors, the risk of inadvertantly introduction is raised due to the retrospective nature of our study.

One criticism that could be argued is that some authors have already described difficulties in defining the point at which the caecum meets the ascending colon, and that is why they are often described as part of a common structure**.** One point that could explain why caecum cancers are described at most advanced stage is that tumors originating from the ascending colon invading the ileo-caecal valvula have probably been included in the caecum's group.

The current scientific advice can not totally eliminate a segmental resection as an oncologically safe procedure which deserves to be explored further.

Conclusion :

In our center, we have not foud statistical differences in length resection from tumors located on the caecum or in the ascendant colon. Tumors located in the caecum were wider than those located on the ascendant colon. The NLNH were similar to the « standard » resection technique but inferior than the CME with CVL. The preoperative localisation was concordant with the ratio observed in the literature.

These findings should be completed by a larger prospective, randomized trail comparing standard resection and CME. Regards to the literature, segmental resection of the caecum with adequate lymphadenectomy should be considerated as an option, but would deserve an other prospective, randomized study.

In our serie, tumors located on the caecum were wider and operated at a more advanced stage.

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Doyen de la Faculté : **M. le Pr. Jean Paul ROMANET**

Année 2016-2017

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POUR LA CONCLUSION DE VOTRE THESE,
INDICATIONS A RECOPIER (*).

THESE SOUTENUE PAR : SIEBERT Matthieu

TITRE : La localisation tumorale des cancers du côlon droit ne modifie pas la longueur de résection colique : Expérience du CHU de Grenoble

Résumé

Introduction : Le cancer colorectal est de plus en plus reconnu comme une entité composée de lésions hétérogènes. Alors que la pratique d'une résection colique gauche segmentaire est acceptée et reconnue, la plupart des auteurs admettent qu'il n'existe pas de place pour une résection colique droite économe pour des raisons oncologiques. La longueur de la pièce de résection colique est toujours sujet à controverse. A notre connaissance, les cancers du caecum et du côlon ascendant n'ont pas encore été analysés séparément. L'objectif de cette étude est d'étudier la longueur de résection colique en fonction de la localisation préopératoire.

Matériel et méthode : Etude retrospective, monocentrique, registre de l'ensemble des patients opérés au CHU de Grenoble entre Janvier 2005 et Août 2016 au CHU de Grenoble d'une colectomie pour cancer du côlon droit. Le critère de jugement principal de cette étude est la longueur de la pièce de résection colique.

Résultats : La tumeur était localisée au niveau du caecum dans 110 cas et au niveau du côlon ascendant dans 119. Il n'a pas été mis en évidence de différence significative entre les deux groupes au niveau de la longueur de la pièce de résection colique (médiane 24 +/-10,34 vs 25 +/-7,28, p =0,95), sur le nombre de ganglions recueillis avec une médiane de 15 (+/- 7,6) contre 15,2 (+/-7,3) (p=0,72). Nous avons identifié 15 cas de discordance entre localisation pré et post opératoire (4 vs 11, p =0,08).

Conclusion : Au CHU de Grenoble, nous n'avons pas trouvé de différence de longueur de résection colique entre tumeurs du caecum et du colon ascendant.

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(*) Grenoble, le 17 octobre 2016

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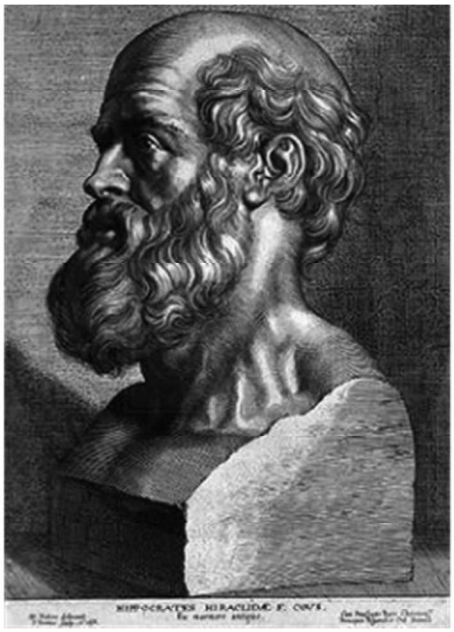
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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

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Mots clés :

Cancer, Colon, caecum, laparoscopie, curage