Review

T_4 Colon Cancer - Current Management

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ABSTRACT: Colorectal cancer is the third most often encountered type of cancer and represents the third leading cause of cancer related deaths, on both sexes. One of the most important prognostic parameters is the tumor's stage at the time of the diagnosis. T4 cancers represent advanced tumors associated with penetration of the visceral peritoneum (T4a) and/or direct invasion in adjacent structures (T4b). Preoperative diagnosis is influenced by the inability of the existent imaging modalities to accurately differentiate the true invasion from the simple, inflammatory adherence to the neighboring structures. As a consequence surgical treatment must follow the principle of en bloc resection; however the ability of achieving an R0 resection depends on the tumor location, invaded organ, and the type of the surgical procedure required. Neoadjuvant treatment for advanced colon cancer it may be very difficult to be applied. This review is focused on preoperative workup, therapeutic strategies and subsequent results in advanced T4 colon cancers.

KEYWORDS: *T_4 colon cancer, extended colon resections, multivisceral resections, preoperative staging, neoadjuvant treatment in colon cancer.*

Introduction

Colorectal cancer is the third diagnosed malignancy among all cancers, both in men and women [1]; in 2012 nearly 1.4 million new cases of colorectal cancer were diagnosed [2]. Also, the colorectal cancer represents the third leading cause of cancer related deaths, on both sexes [1].

The prognostic of a patient with colorectal cancer will depend mainly on the tumor's stage at the moment of diagnosis: the 5-year relative survival rates, in USA, between 2004 and 2010 was 90% in stage I and II (localized disease), 71% in stage III (regional spread), while in stage IV (distant metastatic disease) of only 13% [3].

According to TNM classification of malignant diseases a T4 colon cancer represents a tumor that invades an adjacent organ and/or penetrates the visceral peritoneum; the prognostic role of the T4 colorectal cancer is emphasized by the 7th edition of the AJCC cancer manual which divides the T4 cases in two groups, with different prognosis: T4a if the tumor penetrates the surface of the visceral peritoneum, and T4b if the tumor directly invades or is histologically adherent to other organs or structures; the T4 tumors will be staged as IIB (T4aN0M0), IIC (T4bN0M0), IIIB (T4aN1M0) or IIIC (T4bN1M0) [6,7]. The 5-year disease specific survival for the T4 tumors is about 75.4% [5]; the observed 5-year survival rate, for colon cancer in stage IIB (T4aN0M0) was 60.6%, significantly higher than 45.7% for stage IIC (T4bN0M0) [6,7]. These results emphasize the severity of the tumoral extension to adjacent organs and structures.

The poor prognostic of the T4 colon tumors may be explained by several factors: local extension toward some structures or organs may transform the case in an inoperable one, the high incidence of the lymph node metastases (65.45% in Takano [8] *et al.* study), and due to the increased risk of distant metastases [8-11].

The incidence of the T4 colorectal tumors is around 5-8.8% of the cases [8,12,13]; among the advanced resected cases the incidence of the T4 tumors is up to 21%-43% [13–15]; using the SEER dataset between 1973 and 2008 Gao [6] *et al.*, have found and incidence of 6.3% for pT4a and 4.4% for pT4b colorectal cancers, but only in cases without distant metastasis. It is to be expected that in cases with distant metastasis the incidence of the T4 colorectal cancers to be even higher.

There are several questions concerning the T4 colon cancers that need to be answered: which are the best possible preoperative diagnostic methods for an accurate evaluation of the T stage; which is the best therapeutic strategy in these cases (neoadjuvant *versus* adjuvant therapy); which are the main problems, from a surgeon's point of view?

Preoperative diagnosis and staging

The therapeutic strategy in T4 colon tumors is highly dependent on the preoperative staging and the location of the tumor; preoperative workup includes for TNM staging, in most of the cases, clinical examination, colonoscopy, CEA, abdominal ultrasound, thoracic X-ray, thoracic and abdominal CT (Fig.1) [7,16-18].

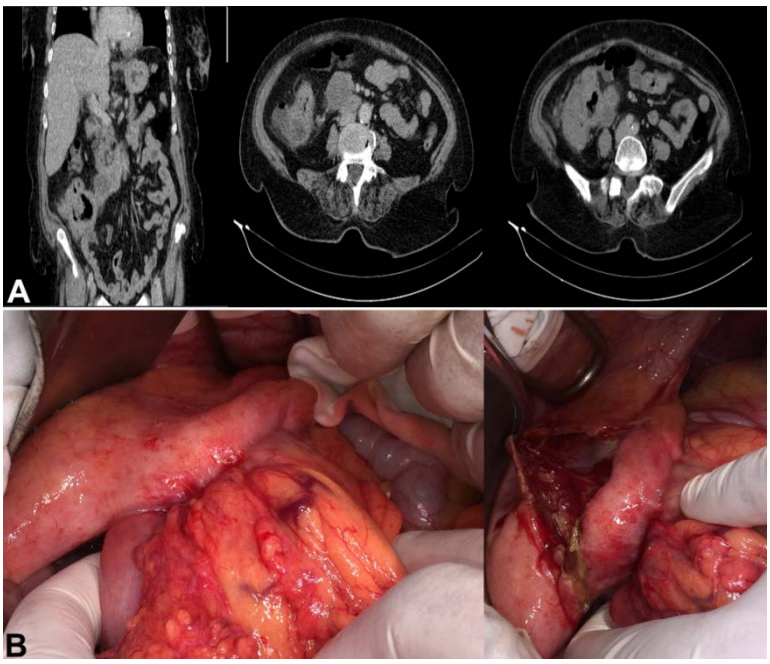

Fig.1. The value of the abdominal CT in the evaluation of the T4 colon cancer. A. Abdominal CT showing the infiltration of the peritoneal fat by a cecal tumor and the disappearance of the cleavage plane with small bowel loops. B. The adherence of the tumor to the abdominal wall was confirmed intraoperatively, but no adherence to small bowel loops or duodenum was found.

From clinical point of view, considering that T4 represents a locally advanced lesion, many of these cases will be diagnosed as emergencies; Grossmann [15] *et al.* have found an incidence of the T4 colon cancer lesions in the emergency cases of 69% compared with 26% in the elective group.

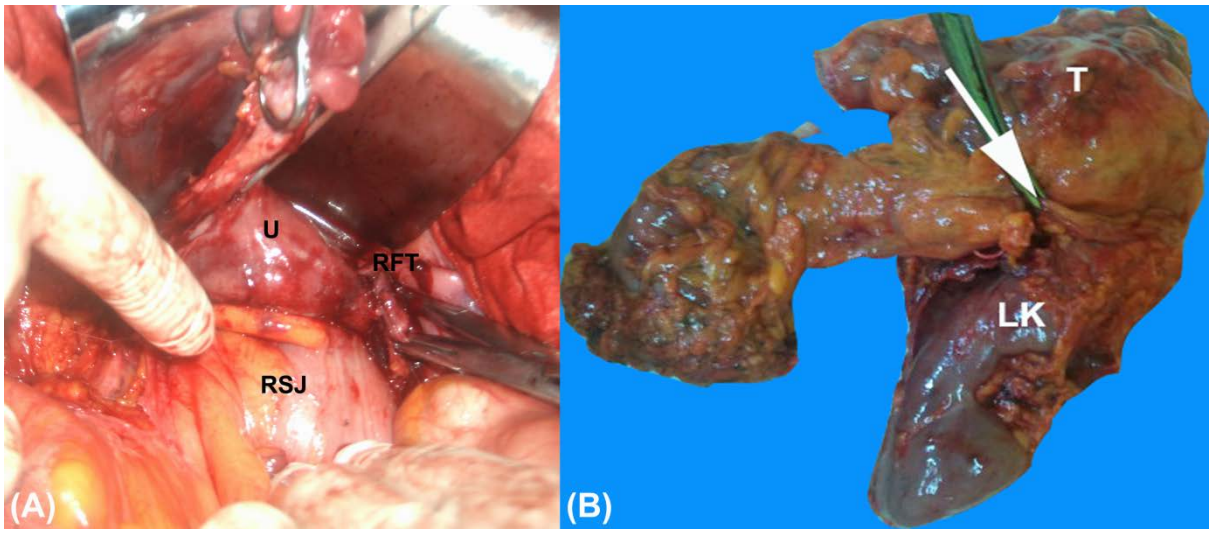

Fig.2. Genitourinary involvement in colorectal cancer: (A). Invasion of the uterus (U) and right Fallopian tube (RFT) in a rectosigmoid junction cancer (RSJ) (intraoperative aspect); (B). Invasion of the kidney (LK) in a left colon cancer (T).

Intestinal obstruction or peritonitis due to the tumor's perforation will limit the preoperative imaging modalities that can be used, and their interpretation may also be affected due to the distended bowel; Grossmann [15] *et al.* have found that preoperative staging was omitted in 30% of the patients with an emergency presentation. However, a preoperative abdominal CT may describe the lesion responsible for the obstruction or perforation and its local extent, and also the presence of the enlarged lymph nodes or distant metastases.

In elective cases it is of paramount importance to establish preoperatively the adherence of the colon tumor to an adjacent organ and the association with synchronous

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metastases in order to create a correct therapeutic and surgical strategy, especially for some tumoral topographies in which demanding surgical procedures may be necessary for cure (Fig.2).

Preoperatively the local extent of the colon tumor is difficult to evaluated; a higher level of the preoperative CEA may indicate an advanced disease, but this is correlated with an important tumoral volume and not with the local extent [19,20].

The main problem of the preoperative staging in colon cancer is that none of the available methods of preoperative staging can 100% predict the T and N stage [14,15,21,22]. For colon cancer the preoperative cT4 diagnosis will be based on abdominal CT; abdominal CT may predict the cT4 stage in 75-86% of the cases [15,21]. Engelmann [14] *et al.* have found an accuracy for CT in staging T4 colon cancer of 70-77%, with a sensitivity of 17-25% and a specificity of 82-93%, not very different from PET/CT (80-82%, 50-58%, 86-91% respectively). In the randomized trial FoxTROT only 47% of the radiologically assessed T4 were confirmed pT4 while 50% of the cT4 were in fact pT3 cancers [22].

It clearly appear that it is place for improvement in the preoperative T and N staging, regardless of the imaging modality selected for the preoperative staging. Nevertheless, abdominal CT is very important in these cases because it draws attention over the extent of the surgical intervention, in cases with tumoral adherence to adjacent organs, but the decision of a multivisceral resection will be made usually after the surgical exploration [23].

The abdominal CT is also very important in the detection of distant metastases, which will greatly influence the therapeutic strategy; in fact, the risk of distant metastases associated with T4 colon tumors is high (up to 45% of the cases), as well as the risk of nodal involvement (up to 65% of the cases) [8,15]. Abdominal CT is very accurate in the detection of the liver metastases, but not for peritoneal carcinomatosis [15], so for the latter situation the final decision will be made intraoperatively.

In the end, the preoperative diagnosing modalities have to answer to several questions: which is/are the directly invaded organ(s) by the T4 colon tumor and may they be safely resected through a potentially R0 procedure? Which is the status of the lymph nodes? Are there any distant metastases? Is the patient general status allowing an extended resection? In fact all of these questions may be reduced to only one: is the patient suitable for an extended R0 resection or a palliative oncologic protocol must be employed?

Therapeutic strategy

Surgical resection of the tumor and invaded organs represents the mainstay of the treatment in colon cancer, but the main problem of a T4b colon cancer is that it is responsible for most of the non-resectable cases. Neoadjuvant or adjuvant protocols may be employed in order to improve therapeutic results: an increased resectability, a lower rate of locoregional and distant recurrences, and an improvement in the functional outcome.

A. Preoperative treatment

In colon cancer there are no well-established neoadjuvant protocols for T4 tumors; considering the fact that colic lumen is narrower than rectal, and the important local tumoral volume surgery will be, usually, required in order to solve or prevent the obstruction, after which the patient will be enrolled for an adjuvant chemotherapeutic regimen. The postoperative chemotherapy for T4N0 tumors (stage II colon cancer) has demonstrated to improve overall survival in some studies [24], while in others not [25]; however, these studies refer to resected cases and makes no comment on the possibility of conversion to operability for non-resected cases due to the local extension of the tumor. In such cases NCCN guidelines 2015 for colon cancer recommend, in suitable patients, an aggressive oncologic protocol in order to obtain conversion to resectability [17].

However, in a phase-2 trial using the FOxTROT regimen preoperatively in advanced T3 and T4 colon cancer a significant downstaging was recorded, with no differences in postoperative morbidity, mortality and hospital stay, compared to a standard postoperative chemotherapy regimen [22]. Also, preoperative chemotherapy was associated with significantly lower proportion of cases with resectional or retroperitoneal postoperative margin involvement [22]. Thus, promising results may arise from neoadjuvant chemotherapy in colon cancer, similar with those for other digestive cancers [22], but remains for future trials to confirm its validity.

B. Surgical treatment: surgeon's concerns

A T4b colon tumor represents always a surgical challenge, at least for some tumoral topography, in which demanding surgical procedures may be required; patient's selection

for these procedures may be also challenging, and in many cases the decision for an extended resection will be taken intraoperatively.

Patient selection for resection. The importance of the patient's general status for the outcome of the colon resections has already been confirmed by the study of Longo [26] *et al.* In T4b colon cancers establishing the patient's fitness for surgery becomes of the paramount importance: an extended pre-therapeutic workup must be employed from cardiovascular, respiratory, hematologic, urinary, hepatic and general nutrition status point of view; a severe dysfunction of any of these organs will contraindicate the resection, due to the high risk of postoperative mortality.

If the general status of the patient allows an extended resection, the presence of distant metastases will influence the therapeutic strategy: if present but operable, the resection must be performed, but only if guarantees an R0 resection. If distant metastases are inoperable (multiple liver and/or pulmonary metastases, metastases with multiple locations) the resection may be employed as a palliative measure, with the condition that the procedure is not too demanding (extensive urinary tract involvement, an extended pancreaticoduodenectomy or hepatectomy required).

Principle of the "en bloc" resection. In advanced colon cancers, with adherence to adjacent organs it is prohibited to detach intraoperatively the tumor from the surrounding tissues, in order to see if truly it is a T4b cancer or the adherence is caused by the peritumoral inflammation; an *en-bloc* resection is preferable to avoid tumoral perforation and neoplasic and stercoral contamination of the peritoneal cavity and also residual malignant tissue.

Even if only 34.4-70% of the tumors adherence is truly a T4b cancer [13,23,27,28], the separation between the tumor and the adjacent organ compromises the oncologic results: 26-100% local recurrence and a poorer 5 year survival (0-30%) [23,27,28].

It is not unusual for a colon cancer to invade two or more adjacent organs, and the incidence of multivisceral resection has been reported up to 12.2% of the colon cancer cases [23]. If possible, all the invaded organs must be resected *en bloc* with the colon cancer, in order to achieve a potentially curative resection, which may be performed in 65% to 85-91.1% of the cases [13,23].

Extended resections in colon cancer. The most frequent involved organs are the bladder and small bowel loops [13,23,29], but depending on the tumoral topography the adherence may interest the abdominal wall, another segment of the colon (Fig.3), the pancreaticoduodenal region, liver, stomach, spleen and/or urinary tract (kidney, ureters, and bladder) and internal genitalia.

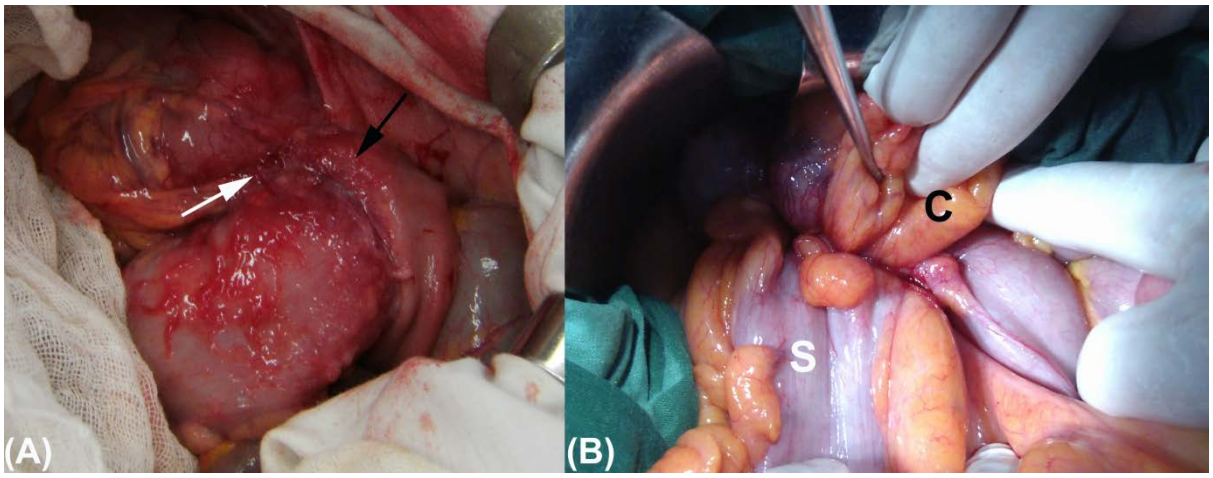

Fig.3. Digestive tube involvement in colorectal cancer (intraoperative aspects): A. Invasion of the ileum in a sigmoid cancer; B. Invasion of the sigmoid in a cecal cancer.

Usually the involvement of the anterolateral abdominal wall doesn't represent a difficult challenge for an experienced surgeon, an *en-bloc* resection of the parietal area of invasion and the tumor bearing colon being the radical solution. Large defect that may results after the resection require in some cases reconstruction using a biological mesh [30]. More difficult to be managed could be the invasion of the posterior wall of the abdomen, mainly because of the other important elements located at this level: major vessels, kidney and ureters, ovarian or

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spermatic vessels; ligation and sectioning of the latter present no real problem, but the invasion of the others may be difficult to be solved in some cases.

Invasion of important vessels represents also an important criterion of non-resectability; invasion of the vena cava in a cancer of the right colon, or invasion of the aorta in a cancer of the descending colon are very rare circumstances, even for these advanced cancers. Invasion of the iliac pedicle is possible in a cecal or sigmoid colon cancer, but more often in rectal cancer. For some selected cases, the resection and vascular reconstruction may be technically feasible, this is not a current practice, and the case is normally considered inoperable.

The kidney and/or the ureter may be invaded both in right and left T4 colon cancer; every time a urinary tract invasion is suspected a preoperative control of the contralateral kidney is mandatory. This can be obtained by an intravenous urogram and/or an abdominal CT, which will show the level and the extent of the invasion, but more important the function of the contralateral kidney.

Usually, an invasion of the kidney and/or ureter will be solved through a nephrectomy [31,32] and/or ureterectomy [31.32], *en-bloc* with the tumor and colon, but whenever it is possible conservative measures must be applied. Obviously, an abnormal function of the contralateral kidney will demand conservative measures over the invaded ureter: an uretero-ureteral anastomosis may be possible [33], but usually the ureter is invaded on important length and the ureteral stumps cannot be sutured without tension. If the upper segment of the ureter is long enough implantation into the contralateral ureter may be also employed, or if possible, re-implantation into the bladder [33]. If these are not possible, a “transplantation” of the kidney in the iliac fossa, may be attempted but this depends on the patient’s general status and the experience of the operating team, this maneuver requiring time, and important notions of vascular and urologic surgery. Although recommended in some retroperitoneal tumors [34], in T4b colon cancer is a very rare circumstance. In some cases resection of the ureter and a urostomy may be the only possibility.

In a cecal or sigmoid cancer, the tumor may adhere to the bladder; the involvement of the bladder may be suspected in the presence of hematuria, or gross invasion on CT. A cystoscopy will confirm the invasion, if the tumor may be visible [35].

In colon cancer the invasion of the bladder may be solved through a partial cystectomy [35,36]. However, the decision of a bladder sparing technique will be based on the possibility of achieving negative resection margins, which depends on the extent of the invasion and its topography; if this goal cannot be achieved a urinary diversion or even a bladder reconstruction may be attempted in selected cases [36,37], but the risk of postoperative complications increases [36].

In female, direct invasion of the internal genitalia may be relatively easy to be solved through an R0 *en-bloc* resection.

Invasion of the small bowel loops is solved through an *en-bloc* enterectomy, while invasion of the other part of the colon (for example invasion of the cecum in a sigmoid or transverse colon cancer, or *vice versa*) requires an extended colectomy, a subtotal colectomy, or even separate colectomies.

A T4 cancer of the transverse colon may invade the stomach, but usually the *en-bloc* resection is not very difficult, through a wedge resection of the greater curvature or a distal gastrectomy [28]. The same is the case for the invasion of the spleen, in a cancer of the splenic angle of the colon, which is solved through a splenectomy or even a splenopancreatectomy, if the tail of the pancreas is also involved (Fig.4).

Invasion of the gallbladder and/or of the liver, in a cancer of the right angle of the colon, may be solved through a cholecystectomy and a wedge or segmental liver resection [28,38], but if the invasion of the hepatic pedicle is present, usually the case is inoperable.

Many discussions are raised by the invasion of the colon cancer into the duodenopancreatic region. Invasion of the duodenum is usually encountered in right-sided colon cancer, but the invasion from a sigmoid cancer was also reported [39]. The limited invasion of the duodenum may be solved through a partial resection of the duodenum [28,38,40]; the resulted duodenal wall defect may be sutured transversely (if small), but if the defect is large it may be covered through an un-open jejunal loop, or a duodenojejunostomy may be necessary [28]. Invasion of a large part of the duodenum, as well as invasion of the pancreatic head, will require a more demanding pancreaticoduodenectomy; in fitted patients, the resection may offer the chance for cure, with a better prognosis than for palliation [27,41,42].

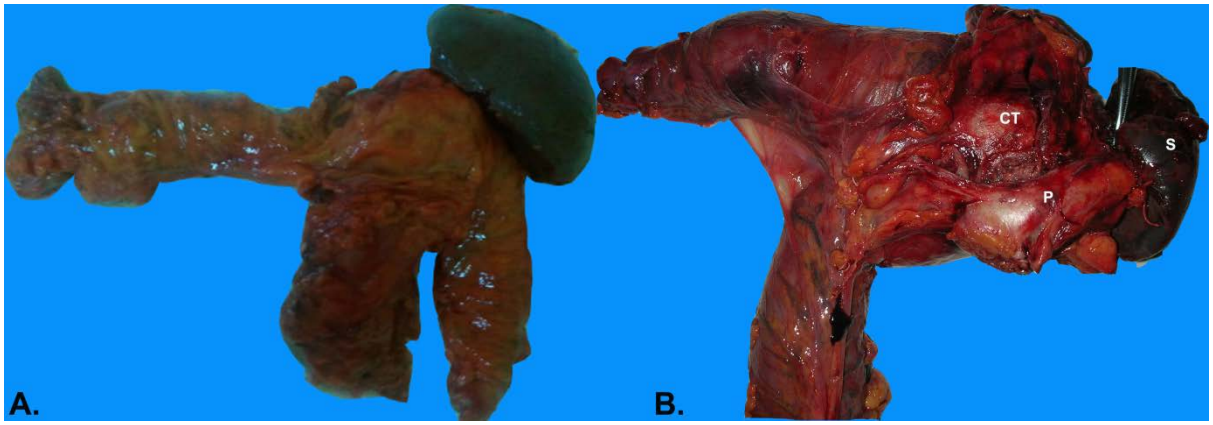

Fig.4. Invasion of the spleen and pancreas in colon cancer (intraoperative aspects): A. Invasion of the spleen in a left angle colon cancer; B. Invasion of the spleen and pancreatic tail in a left colon cancer.

Expected results in T4 colon cancer

Postoperative morbidity and mortality after extended resections for colon cancers will depend on the patient general status, the type of the resection, and the number of the involved and resected organs, due to specific complications.

The long-distance survival in T4 colon cancer is greatly influenced by the age and the patient preexisting co-morbidities, the therapeutic strategy (neoadjuvant and/or adjuvant treatment), and the possibility to achieve an R0 resection.

Although not all of the studies have shown a significantly influence of the surgeon on the outcome after curative resections for colon cancer [42], a T4b colon cancer may require demanding procedures, in which the surgeon skills may have a great influence on the outcome, both from postoperative morbidity and mortality, but also in terms of long distance survival.

The 5-year relative survival rates for T4 colon cancer varies from 79.6 (T4a) or 58.4% (T4b) in case of no lymph node involvement (N0), to 40.9-54% in case of nodal involvement for T4a category, but significantly lower for T4b category with nodal involvement (15.7-38.5%) [6,7,44].

In a secondary analysis, a different prognosis was discovered for T4a and T4b colon tumors: in T4a the observed survival at 5 years was 60,6% if N0 and 26,6-47% if N+, while in T4b the observed survival at 5 years was 45,7% if N0 and 15.8-27,9% if N+ [45].

These results were extremely important because have demonstrated a significant difference between the T4 categories, with a poor prognosis if the colorectal cancer invades adjacent organs or structures (T4b); this may be explained because the immediate postoperative results, but also distant results, are greatly influenced by the organ or structure which is involved, and what the extended resection presume.

In urinary tract involvement the postoperative morbidity was reported as 41% of the cases, with a postoperative mortality of 5% [31].

Duodenal resection implies specific postoperative complications (duodenal leaks, duodenal stenosis) which may appear with a frequency of 23% [40], but resection of the duodenum may result in good long distance results, with 61.5% of the patients surviving at 3 years, and 30.76% reaching 5 years after the en bloc resection [40].

Pancreaticoduodenectomy associated to a right colectomy is reported in small series and it will increase postoperative morbidity (up to 60%) [42] and mortality up to 14.28-16.67% [27,28,41,46]. However, resection of the pancreatic head was associated with 60% survival at 2 years, and 21.42% tumor recurrence in the study of Zhang [41] *et al*, with a median survival of 54 month, much better than for palliation [42]; Saiura [46] *et al*, reported also an overall survival rate of 55% at 5 years.

Most authors agree that the presence of the obstruction or tumoral perforation is associated with a shorter 5-years survival; however, for T4 colon tumors it is not clear if the long-distance prognostic is influenced by the presence of the complication itself or by the advanced stage at presentation [47,48]; probably both factors have a contribution on these worse results: a locally advanced tumor is associated in a larger proportion of cases with lymph node involvement and the presence of distant

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metastases [15], while the presence of the complication reduces the therapeutic options. Although the tumoral stenosis or perforation doesn't necessary predict a T4 lesion (the inflammation associated with a T3 or even T2 colon cancer may be an important associated factor), it is recognized that in such cases the incidence of the T4 cancers (up to 69%) will be higher than for elective cases [15].

As a consequence, along with the biological alteration, the treatment will have in most of the cases as starting point the surgery, with the main objective of solving the complication; thus extended resection, necessary in case of a T4b colon tumor will be often avoided, and in many cases the primary operation will be a derivative one [49]. The possibility of solving the obstacle endoscopically may be of real help, allowing a more accurate preoperative diagnosis, and after the general status of the patient is alleviated, a curative procedure; however in T4 tumors the applicability is limited and not without risk [49,50].

The presence of the tumor's perforation will impose emergency surgery, usually a Hartmann resection being performed, if possible, otherwise a supra-tumoral colostomy or an ileostomy with peritumoral drainage being the only surgical possibility; in spite of up to 9-12% postoperative mortality, an aggressive management is recommended, leading to a 58% adjusted 5 year overall survival [47,48].

On the other hand, the long-term prognosis in perforated tumors may be affected by the possibilities of tumoral implantation on the peritoneal surface, or even the operative incision. In fact, Temesi [51] *et al.* have found that even non-perforated T4a tumors are associated in 75% of the cases with positive peritoneal lavage cytology, and this circumstance is associated with an increases risk of locoregional recurrence and distant metastases (56% in positive cytology group *vs* 23% in negative lavage cytology group) [51]. On a median follow-up of 34.8 month, Hompes [52] *et al.* have demonstrated a risk of peritoneal carcinomatosis for T4a colon cancers of 50% and of 20% for T4b tumors, proposing as prevention adjuvant hyperthermia and intraperitoneal chemotherapy for these stages [52].

Nevertheless, the obstruction or perforation itself it's not a counterindication for an extended resection if the patient is suitable; Lehnert *et al* [23] have reported 17% extended resection for emergency presented colon cancer.

Extended resections in T4 colon cancer may also be approached laparoscopically but, as expected, with an important percentage of conversions [13,53].

All these results emphasize that in spite of the increased postoperative morbidity and mortality of the extended resections, the better long-distance results of the resection, compared to palliation, recommend an aggressive approach in T4 cancers.

Points of debate

An important question is if the resection of the invaded organs must obey the oncologic principles, due to the risk of metastases in the adjacent lymph node area, or the resection may be limited to the involved organs? Usually extended resection will include only the organ at which the colon cancer adhere, but whenever enlarged lymph nodes draining the involved organ are identified they must be biopsied and if possible removed. Multivisceral resections are associated, however, with an increased number of harvested lymph nodes [13] and there is no evidence that an extended lymph node dissection will improve the local recurrence and/or distant survival rates.

Conclusions

The preoperative staging in colon cancer has considerable improved with the advancements in imaging modalities; however, preoperative diagnosis of a T_4 colon cancer may be difficult due to the important percentage of cases presented with intestinal obstruction or tumoral perforation and due to the inability of these imaging modalities to accurately predict the true malignant invasion.

The role of neoadjuvant treatment in T4 colon cancer is not well established for improved the resectability and survival rates.

Extended resections must be employed in T_4 colon cancers, with acceptable postoperative morbidity and mortality, but are conditioned the possibility of achieving an R_0 resection and must obey the principle of *en bloc* resection.

In spite of the considerable advances in preoperative staging and therapeutic strategy in T_4 colon tumors is place for future improvements; also, some points of debate will require further clarifications.

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