CHAPTER 5
Surgical treatment: general concepts

Time of surgery

Curative intent colectomy should be performed without delay after diagnosis. Evidence IC.[1] According to a retrospective analysis by Surveillance, Epidemiology and End Results (SEER) and the National Cancer Database, delaying surgery by 3 to 6 weeks was associated with decreased OS. However, a Canadian population-based retrospective study indicated that delaying surgery by up to 12 weeks does not affect disease free survival (DFS) or overall survival (OS).[1,2]

Since a specific interval for the timing of surgery cannot be established and evidence supports that untreated cancer progresses over time, surgery should be performed without delay.

Once surgery has been decided, surgical exploration includes visual inspection, and in open surgery, palpation to detect synchronous lesions or more advanced malignant disease, for example involvement of neighbouring organs or peritoneal metastases. If the latter are identified incidentally, a biopsy is recommended to confirm the diagnosis and ideally classify them according to the *peritoneal cancer index*.

In the event of obstruction or perforation, both colectomy and cytoreduction surgery should be deferred for a multidisciplinary discussion of the best therapeutic option.

For this reason, a thorough examination should be performed at the time of surgery and documented in the procedure report. Evidence IC.[1]

Extent and type of resection

According to a recent study, the presentation was Stage I: 25.7%, Stage II: 17.4%, Stage III: 11.7% and Stage IV: 35.6%.[1–6] The extent and type of colon resection correspond to the lymphovascular drainage of the organ. Evidence 1B.[1]

The mesocolon to be resected corresponds to the primary nutrient vessel at its origin in order to remove the central and intermediate nodes. The resection must be performed preserving the integrity of the mesocolon. This concept will be developed in more detail in the section on complete dissection of the mesocolon.

The number of lymph nodes removed has been associated with a change in survival, so their examination is important and should be performed as thoroughly as possible. Histopathological evaluation of at least 12 lymph nodes is recommended to classify tumors as N0. If fewer than 12 nodes are examined, the cancer is considered Stage II high-risk.[3,6]

The most commonly used surgical procedures are hemicolectomy and subtotal colectomy, followed by partial or segmental colectomy. In an institutional experience, the Italian Hospital of Buenos Aires reported 1549 consecutive patients operated on in 25 years: 528 right colectomies, 79 extended right colectomies, 556 left colectomies, 18 anterior resections and 74 subtotal colectomies. Resectability was 95.8% and primary anastomosis was performed in 97.4%. Postoperative morbidity was 18.6%, anastomotic dehiscence 1.4% and mortality 3.4%.[7]

Resection margins

Treatment of both the distal and proximal margins should be considered. Nodal metastases occur along the marginal artery in the epicolic and paracolic nodes, followed by the intermediate and apical or central nodes at the origin of the main artery. The oncologic outcome depends on whether colectomy ensures radical nodal resection. Historically, a 5-cm margin on either side of the lesion was considered sufficient.[8] However, today, to achieve adequate total mesocolonic excision with or without D3 lymphadenectomy, this margin must be wider and reach a minimum of 10 cm on either side. These concepts are developed in more detail in Chapter 6.

Vascular anatomy

The small intestine, the right colon, and the proximal two-thirds of the transverse colon are supplied by the superior mesenteric artery, while the inferior mesenteric artery supplies blood from the distal segment of the transverse colon to the rectum. Anatomical vascular variability is present mainly on the right side, while on the left side it tends to be more constant. The ileocolic artery is constant, but may run anterior (17 to 83%) or posterior to the superior mesenteric vein. The right colic artery may arise from the ileocolic artery or the middle colic artery and is present in up to 60% of cases. It divides into right and left branches, both of which are inconstant and may be absent, double, or have an accessory artery.

There are several anatomical and clinical studies of vascular anatomy and its variants with the aim of determining preoperatively the type of resection to be performed.

Okazaki et al.[9] from the University of Tokyo studied the arteries of the transverse mesocolon and its equivalent in 60 cadavers using software. The arteries of the splenic flexure were evaluated, finding 34 arterial variations, most of which were from the superior mesenteric artery and the middle colic artery, with its typical course below the pancreas. Another arterial course was identified that originates behind the caudal pancreas, crosses the mesocolon and moves away from the pancreas to head towards the splenic flexure. The course could not be determined by tomography. It was concluded that for the first time two types of arterial courses were shown towards the splenic flexure (below the pancreas and within the mesocolon). Complete excision of the mesocolon is probably performed more easily in the second variant.

Central vascular treatment

Central vascular ligation is key in the resection and oncological prognosis of colon cancer treatment. Its basis is the resection of all lymph nodes at the central level. According to Patrón Uriburu,10 central metastasis can occur in 11% of right colectomies and in 8.6% of left colectomies. There is a phenomenon called *skip metastasis* or discontinuous metastasis, which consists of the presence of central lymph node metastasis having skipped the intermediate lymph node stations, which occurs in approximately 2 to 4% of cases.

At this point it is important to remember that the dissection of the epicolic nodes is defined as D1, that of the intermediate nodes as D2 and the central one as D3.[11–13]

According to the available evidence, there is a direct relationship between the depth of invasion (T) and lymph node involvement (N). In T3 and T4 tumors, central lymph node metastases can be found in 8%, while they are almost nonexistent in T1 and T2 tumors. For some authors, resection of the central lymph node level has oncological results equivalent to curative resection of liver metastases.[14]

Lymph node dissection and lymphadenectomy

Theories on lymph node dissemination

The lymphatics follow the course of the arteries and the nodes are classified as epicolic (located in the wall of the colon), paracolic (along the marginal artery of Drummond), intermediate (arranged along the main vessels) and central (located at the origin of the superior and inferior mesenteric arteries).

To evaluate lymph node dissection, it is necessary to take into account the different theories that have been proposed to explain metastatic lymph node dissemination, namely:

- In 1907, Halsted assumed that the tumor spreads first to regional lymph nodes and then to different organs. This evolved into the concept of sentinel lymph node and its biopsy as a staging tool, particularly in the adjuvant setting of breast cancer.[15]
- Fisher believes that both lymph node dissemination and distant metastasis occur in early stages. However, the complexity of lymph node metastasis in colon cancer may not account for either of these cases.[16]
- Zhang in 2020 analyzed different routes of dissemination using genomic sequencing. Of 61 possible pathways of lymph node metastasis, 34% were *skip metastasis*.[17]

Types of lymph node dissection

The types of lymph node dissection according to the Japanese doctrine are:

- D1: Complete dissection of the epicolic lymph nodes along the colon and the paracolic nodes along the marginal artery, without dissection at the level of the intermediate and main arteries.
- D2: Complete dissection of D1 and of the intermediate lymph nodes along the main nutrient arteries (ileocolic, right colic, middle colic, left colic, sigmoid and inferior mesenteric artery from the origin of the left colic artery to the origin of the last sigmoid artery).
- D3: Complete dissection of D1, D2 and of the central lymph nodes. For left-sided tumors, lymph nodes are resected along the inferior mesenteric artery between the aorta and left colic artery and for right-sided tumors and those medial to the transverse colon, lymph nodes are resected along the superior mesenteric vein and lateral to the superior mesenteric artery.
- D4: Complete dissection D1 to D3, along the aorta and inferior vena cava or the superior mesenteric artery, superior mesenteric vein, central to the origin of the middle colic artery. An alternative definition of lymph node involvement includes:
- N1 (+): Metastatic lymph nodes in area D1, within 5 cm proximal and distal to the tumor margins.
- N2 (+): Metastatic lymph nodes in area D2, greater than 5 cm proximal and distal to the tumor.
- N3 (+): Metastatic lymph nodes in area D3.
- N4 (+): Metastatic lymph nodes in area D4 (consider distant metastasis).

According to the Japanese Society for CRC guidelines, mesocolic regional lymph nodes are classified as pericolic or D1 (confined to the marginal colic artery), intermediate or D2 (located along the trunks of the ileocolic, right colic, middle colic, left colic, sigmoid, and inferior mesenteric arteries), and apical or D3 (at the root of the ileocolic, right colic, middle colic, and inferior mesenteric arteries).[4]

Multiple centers are emphasizing the combination of central vascular ligation (D3 lymphadenectomy) and total mesocolon excision to achieve a better quality specimen and a better prognosis. The number of positive lymph nodes is a prognostic factor associated with stage, recurrence, and survival.

Rarely, lymph node metastases occur at sites distant from the primary tumor, with negative pericolic or intermediate nodes (*skip metastasis* described in gastric, thyroid, lung and breast cancer), which has a variable impact on survival depending on the type of cancer. Its incidence in colon cancer is variable, ranging from 2 to 9%, with some reports of up to 13.2%.[18–24]

For some authors, D3 lymphadenectomy in patients with Stage III is useful not only for lymph node staging but also to identify *skip metastases* to improve survival.[25–29]

Japanese guidelines classify lymph node involvement into three levels: L1 (epicolic and paracolic node involvement), L2 (intermediate node involvement), and L3 (central node involvement). In a study of 446 patients with stage III colon cancer, routine D3 lymphadenectomy found 6% L3, 25% L2, and 70% L1 involvement, with the number of nodes removed being 44, 40, and 42, respectively.[4]

According to ESMO and Japanese guidelines, the decision on the type of colectomy and corresponding lymphadenectomy is based on clinical findings, the presence of lymph nodes and the depth of tumor invasion, observed preoperatively.[3,4] The recommendations of the Japanese guidelines on the type of dissection indicated according to the depth of tumor invasion and lymph node involvement are detailed in Figure 5.1.

Lymph node metastases outside the standard resection territory occur in 3 to 11% and are more frequent in advanced stage tumors.

Central lymph node involvement in the absence of pericolic or intermediate lymph node involvement (*skip metastasis*) occurs in up to 4% of cases.[4,19,30]

According to a study from Taiwan, the group of tumors with *skip metastasis* had a worse prognosis in pN1 tumors.31 In the pN2 stage, a worse survival rate was not evident between both groups. Furthermore, in pN1 tumors the lymph node ratio (LNR) could be less important than the location of the positive node in the mesocolon. On the contrary, in pN2 tumors the LNR could be interpreted as a greater tumor volume in the lymph nodes and affect the lymph node distribution more strongly.

Extended lymphadenectomy with central vascular ligation (D3 resection) has demonstrated higher LNR and probable improvement in pN staging, but is also associated with increased intra- and postoperative complications. Furthermore, observational studies and meta-analyses suggest that extended lymphadenectomy decreases the incidence of colon cancer recurrence and improves recurrence-free survival.[28] In contrast, other studies have failed to determine survival benefits.[30] The ASCRS practice guidelines do not recommend routine extended lymphadenectomy, but rather selective dissection of clinically positive or suspicious nodes located outside the site of routine lymphatic drainage. Evidence 2B.[1,2] The term “complete mesocolon excision” is not synonymous with D3, but refers to the integrity of the mesocolon and its surrounding peritoneal layer after resection. That is, it refers to the type of resection and does not designate a specific level of vascular ligation or lymph node dissection.

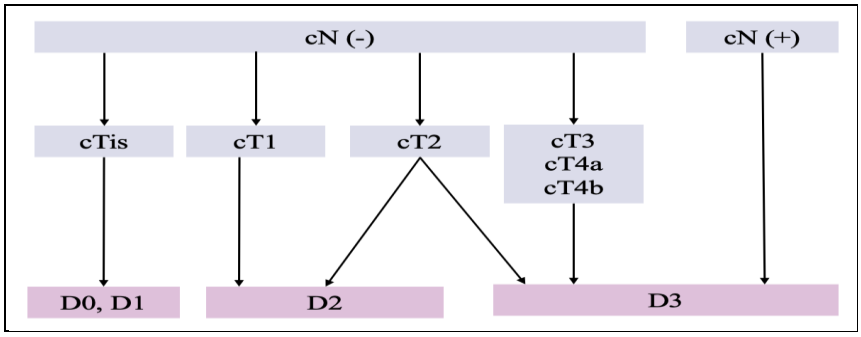

Figure 5.1. *Dissection according to preoperative T and N staging, recommended by Japanese guidelines.*[19]

Indications for the type of dissection according to the tumor stage

According to Japanese guidelines, for cTis tumors the recommended dissection is D0, since they do not present lymphatic metastases. However, if for some reason a colectomy is performed to treat a Tis, the D1 dissection is sufficient. The D2 dissection is recommended for cT1 tumors, since in these the incidence of lymphatic involvement is 10% and approximately 2% present involvement of the intermediate nodes. For cT2 tumors, despite the scarce evidence, it is recommended to perform at least a D2 dissection. However, a D3 dissection may also be indicated since approximately 1% are accompanied by positive main nodes and the exact determination of the depth of tumor invasion with the available study methods is incomplete. For tumors clinically classified as T3, T4a and T4b, colectomy should be associated with a D3 dissection.[4] The distribution of the three lymph node stations of the right and left colon is schematized in Fig. 5.2.

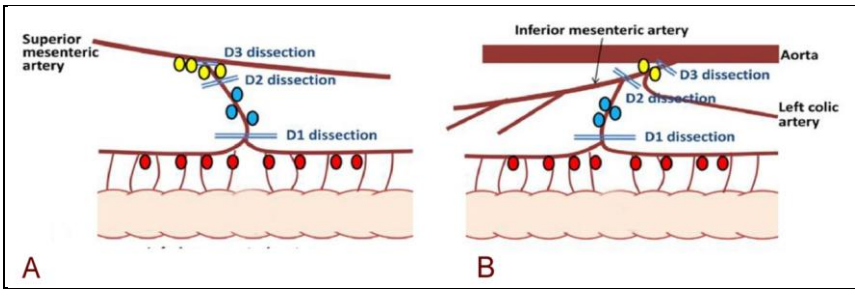

Figure 5.2. *Lymph node stations for right and left sided tumors.*

If macroscopic or suspicious lymph nodes are present as an intraoperative finding, the Japanese guidelines recommend performing a D3 dissection. If there are no visible or identifiable lymph nodes on intraoperative or preoperative studies, the lymphatic dissection to be performed should be based on the depth of the tumor. These guidelines detail the incidence of lymphatic metastases according to the depth of invasion.[4]

In D1, D2, and D3 dissections, resection of the colonic margins is determined by pericolic lymphadenectomy. This lymphadenectomy is defined by the positional relationship between the primary tumor and the feeding artery. Lymphatic metastases at a distance of 10 cm or more from the tumor edge are rare. A Japanese multicenter nationwide study investigating the distance between the primary tumor and lymphatic metastases is ongoing. Unlike what occurs in the rectum, in the colon there is no evidence on the distribution of lymphatic metastases in T4, N2 and M1 tumors, which are usually located at a significant distance from the primary tumor.

Unlike what the Japanese guidelines recommend, for other authors and guidelines there is no clear evidence on what type of lymphadenectomy to perform according to the location of the tumor and the corresponding lymphatic territory. The main controversy exists in the indication of a D2 or D3 type dissection. There is a direct relationship between the number of resected nodes, the involved nodes and survival; the greater the number of resected nodes, the greater the survival. While the Japanese guidelines recommend extended D3 type lymphadenectomies as the standard for tumors ≥ T3 without taking into account node involvement, in the West this is not a standard procedure.

Laparoscopic surgery for transverse colon cancer may be a feasible technique. In a retrospective study from a Japanese center, 252 patients who underwent laparoscopic surgery for transverse colon cancer were analyzed. The transverse colon was divided into 3 segments by performing a right colectomy, a transverse colectomy, and a left colectomy. The frequency of metastatic lymph nodes was 28.2, 19.2, and 19.2%. *Skip metastases* occurred in right- and left-sided transverse colon cancer, but not in the middle segment. The 5-year OS rate was 96.3, 92.7, and 93.7%, and the relapse-free survival rates were 92.4, 88.3, and 95.5%, respectively. In multivariate analysis, the only independent risk factor for recurrence-free survival was the absence of lymph node metastasis.[32]

The oncologic outcomes of D3 dissections have been encouraging. A 5-year OS of 90.4% was reported with open surgery and 91.4% with laparoscopic surgery. Laparoscopic D3 resection was noninferior to conventional resection in terms of OS for patients with Stage II and III colon cancer. OS was similar and better than expected, so laparoscopic surgery might be acceptable for the suggested treatment.[33,34]

The COLD trial[35] compared D2 and D3 dissection, demonstrating that the latter is a feasible and safe technique,

with similar 30-day morbidity and better surgical specimen quality. For Patrón Uriburu et al.[10] it would be sufficient to perform an adequate D2 dissection in all cases and reserve a D3 dissection for selected cases.

In a conference given at the Argentine Academy of Surgery, Vaccaro[36] concludes in his final comments:

- An adequate D2 dissection is associated with a low local recurrence and it is advisable to audit one's own results.
- D3 dissection is safe when performed by experts, with no advantages to date in Stages I and II.
- The overall advantage is controversial, with contradictory evidence in non-systematized D2 dissections.
- Not all Stage III would benefit, considering tumor biology, aggressiveness and response to chemotherapy.
- Systematic use in groups with good results implies a high number of patients to treat without clear evidence.
- Selective use by experts could be justified in young patients with advanced tumors.

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