



Colon and rectal cancer oncoguia

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PART I. PROCESS AND METHODOLOGY OF THE CLINICAL PRACTICE GUIDELINES IN CANCER-ONCOGUIDES

PROCESS

Introduction

The OncoGuies are the tool used by the Oncology Master Plan to accomplish therapeutic equity. The Department of Health and Social Security of the Autonomous Government of Catalonia has deployed the Oncology Master Plan of Catalonia which, amongst other objectives, establishes that measures for the improvement of cancer attention based on the best possible scientific evidence should be developed. The management of this Master Plan has been commissioned to the Catalan Institute of Oncology (ICO), a public company whose missions include providing assessment to the CatSalut - Catalan Health Service in the prevention and control of cancer in Catalonia as well as in the improvement of cancer care to the population.

Actors

The use of an OncoGuia has to guarantee that the treatment recommended by scientific studies and treatment and experts from all over the world involved in this type of disease is received. To accomplish this purpose, it was decided that the health administration would play a dynamising role, and that the fundamental actors and those responsible for the development of the aforementioned OncoGuies would be health care professionals, with the methodological support of the CAHTAR.

The Tumour Commissions and the departments of Medical Oncology, Haematology, Radiotherapy Oncology and Surgery; medical and surgical specialities such as Digestive, Endoscopy, Pneumology, Gynaecology, Plastic Surgery, Thoracic Surgery; as well as specialists in Central Services, Pathology, Radiology and Nuclear Medicine of the hospitals of the Public Use Hospital Network of Catalonia, are the participants. They all provide the clinical experience materialised in the existing protocols of the main types of tumours and, in the corresponding phase of the process, revise and debate the preparation of the algorithm and the wording of the text of the OncoGuies to achieve a definitive document, and are an

On the other hand, the objectives of the *Catalan Agency For Health Technology Assessment and Research* (CAHTAR) of Catalonia also include the generation of information based on the rigorous and systematic analysis of scientific evidence, so that health system decision-makers will be able to act on the basis of the best information available. In this regard, the CAHTAR has broad experience in the conduct and assessment of Clinical Practice Guidelines.

These objectives and missions crystallised in the signature of an ICO-CAHTAR agreement to create a joint programme called Programme of Clinical Practice Guidelines in Cancer-OncoGuies, whose basic features are quality, efficiency and transparency.

Expert Committee that will make sure that the aforementioned OncoGuies are permanently updated. This part of the process is fundamental in establishing the dynamics of participation and consensus that will make the final document the product of everyone and the property of the experts and Agencies commissioned to produce it.

The CAHTAR has systematically compiled and reviewed and assessed the quality of the national and international clinical practice guidelines available on the types of cancer in question. It has also evaluated the quality of the health-care protocols in force in Catalonia with regard to the degree of evidence that supports them and the extent to which they are endorsed by the experience reviewed. Subsequently, it drafted the corresponding guides, which were debated in different working days organised for this purpose, both with professionals from the different Catalan institutions and experts from abroad. The main international guides evaluated were those of the *National Comprehensive Cancer Network*, the *Fédération Française de Centres of Lutte Contre le Cancer*, *Cancer Care Ontario* and the *National Institute for Clinical Excellence*.

Moreover, the Academy of Medical Sciences of Catalonia and the Balearics provide their scientific support while coordinating the preparation of the general recommendations for the drafting of pathological reports by means of Catalan Society of Pathology.

The OncoGuides are based on state-of-the-art scientific knowledge, the revision of international experience and the inputs of experts

from our setting, profiling and establishing their applicability in our health setting. Therefore, they will make it possible to guarantee receipt of the best and proven treatment, regardless of the place of residence. It should be mentioned that in this case the innovation lies in the standardisation of these treatments. The attributes of equity, protection and consensus are those which most faithfully reflect the utility of the OncoGuides.

Content

The main quality is the fact that they are basic and clear. The standard guide has the following composition:

- Expert committee involved
- Process and methodology of preparation
- Algorithms of diagnosis, treatment and follow-up
- Explanatory text
- References

A data base of outcomes results with indicators of oncological care (disease-free survival, overall survival, number of nodes analysed,

and others specific to the type of tumour) will be added. This data base will be a differential and innovative addition with regard to the other international clinical practice guidelines in place at the moment. It will act as a quality control apparatus and as an indicator of the need to update the OncoGuides.

The qualitative objective is to make reliable and integrating OncoGuides, which can compete in quality and universality with any of those regarded as reference guidelines in the different social and health environments.

METHODOLOGY

Link of the recommendations to available scientific evidence

In the algorithms of the OncoGuides, a series of diagnostic, preventive or therapeutic interventions are proposed for different types of tumours. To decide the recommendations for each one of the cases, the existing protocols and current clinical practice in the different Catalan hospitals were taken into account, as were the opinions and arguments of the members of the different task forces expressed at a series of open meetings and programmes within a structured plan of work. The basic working method was the preparation of preliminary documents which were discussed and were not regarded as definitive until a consensus was reached by the group of experts. The members of the task forces raised different considerations on the various drafts (in written or at the actual meetings) which were discussed in all cases at the scheduled meetings.

For a series of recommendations selected by each task force, according to their relevance, two additional tasks were added. In the first place, the degree of agreement on the recommendation in the task force was verified, and

a category was assigned within a classification of the degree of consensus. Secondly, a brief synthesis of the available scientific evidence supporting the operation was performed, with the assignment of a category inside a classification according to its quality.

Thus, each one of these selected recommendations are mentioned in the algorithms with two values: one pertaining to the degree of consensus in the task force and another pertaining to the quality of the scientific evidence supporting it; usually, there is a reference to a text which briefly synthesises the evidence. The process and the categories of both classifications are described below. The classifications have been drawn up taking the current proposals of the *National Cancer Institute* into account (www.cancer.gov/cancerinfo/pdq/), the *National Comprehensive Cancer Network-NCCN* (www.nccn.org/), the *NHS Scotland* (www.show.scot.nhs.uk/sign/guidelines/), the *Institute for Clinical Systems Improvement-ICSI* (www.icsi.org/), the *Fédération Nationale des Centres de Lutte Contre le Cancer* (www.fnclcc.fr/) and the *CAHTAR* (www.aatrm.net)

Classification of the scientific evidence available

Most of the current classifications use the susceptibility to bias of the design of the studies that support the efficacy of the intervention in question as a basic element. Generally speaking, they concede the highest level of the classification to studies in which the assignment of patients in the different groups was random (normally controlled and randomised clinical trials or meta-analyses of clinical trials with these characteristics), and the minimum level to the opinion of experts in the absence of higher-level evidence. In intermediate classifications, there are the analytical observational epidemiological studies with a control group (for example, cohort or case and control studies) and observational studies without a control group (for example, case series).

As has just been commented, most classifications assess fundamentally evidence on the efficacy of the operation addressed and do not formally assess questions related to the risk of iatrogeny, or the convenience of the operation or its costs. Accepting, as an initial approach, that efficacy must be taken into account first, in the specific case of oncology it was felt that it was basic that the classification reflect what the variable of efficacy measurement used in the studies that support the operation in question was, since a measure that has demonstrated survival is regarded as superior to one that has only been shown to improve tumour response rate.

Classification of the degree of consensus

Category E	Standard. When the task force agrees that the operation posed in the specific context of the algorithm is recommendable.
Category OC	Consensus option. When the majority (90%) of the task force considers that the operation posed in the specific context of the algorithm is recommendable.
Category O	Option. When there are major discrepancies as to whether the operation is recommendable and there is no majority consensus in the task force.

It must be remembered that, with a certain frequency, for the same population different operations may be available on which there may have been different degrees of consensus in the same task force.

Classification of the available evidence

Category 1	Experimental studies with random assignment (randomised clinical trials or meta-analyses of these clinical trials)
Category 2	Observational studies with control group (cohort studies, cases and controls studies)
Category 3	Observational studies without control group (case series)
Category 4	Expert opinions

A letter is added to these categories depending on the main endpoint variable used in the studies that support the efficacy of the operation:

A	Total mortality
B	Mortality by cancer
C	Quality of life
D	Indirect measures (disease-free interval, disease progression-free interval, rate of tumour response)

Thus, each one of the selected recommendations has been classified into a series of levels that range from a maximum of **1A** to a minimum of **3D**; when the recommendation was based only on the expert opinions it made no sense to assign the corresponding letter to the primary endpoint.

It must be remembered that, with a certain frequency, different operations supported by scientific evidence that may be of different quality and therefore be classified within different levels may be available for the same population.

Limitations of the method used

Classification of the degree of consensus

No formal votes were made in the task forces, and the degree of consensus was estimated by the group coordinator in charge of gradually adding the classification of the scientific evidence available and the degree of consensus for each one of the operations selected. Subsequently, the provisional classification

of the degree of consensus for each operation was confirmed or modified, accordingly, at the task force meetings.

No specific method has been defined to move from the classification of the available scientific evidence to the recommendation for each selected operation; no explicit criteria were defined to consider the aspects mentioned in the preceding section (for example, magnitude of the benefits, the risk of iatrogeny, etc.), neither were the costs nor the aspects related to the convenience of the operations (for example, complexity or the need for specific monitoring). Some of these aspects were often addressed by the task force on the basis of the evidence, sometimes contradictory, which impacted the degree of consensus reached. In the future, an assessment will be made to modify the method to go from the classification of the available evidence to making recommendations and establishing the degree of consensus.

Classification of the available evidence

The basic criterion of the classification was susceptibility to bias of the design of the studies supporting the operation, but no scale was used to measure the specific quality of each one of the different types of study in greater detail or the heterogeneity of the results between different studies. On the other hand, focus was placed on the efficacy and the primary measurement endpoint, but did not formally address the magnitude of the benefits or the uncertainty as to the estimate of efficacy (precision of the measure). Neither was the risk of iatrogeny or toxicity of the operation included in the formal assessment. Many of these additional questions were addressed in some of the task force discussions and had a bearing on reaching a larger or smaller degree of consensus on the recommendation of each one

of the operations. In the future, an assessment will be made as to whether formally adding some or any of these questions to classify the evidence or gage the strength of the recommendations is worthwhile.

Another limitation was that no explicit criteria were defined to identify and select the available scientific evidence for each operation selected. For each one of them, specific members of the groups of experts made a scientific evidence summary proposal, with the corresponding bibliographic references, and an initial classification proposal; both proposals were submitted to discussion, and modification, as appropriate, by the task force. In some cases, the scientific evidence collected in other published recommendations or clinical practice guidelines were taken into account. In the future, the aim is to maintain a small group of experts for each guide which, among other tasks, will identify and select new scientific evidence according to its relevance to confirm or change the recommendations made in this first edition. An assessment is made as to whether formally adding explicit criteria to identify and select the scientific evidence is worthwhile.

Finally, it must be mentioned that the classification used is particularly suitable for preventive and therapeutic interventions, but would probably need to be adjusted for diagnostic or prognostic interventions. Despite this limitation, and taking into account that a substantially complex project was being undertaken, and that the majority of interventions selected to be linked to the available scientific evidence are therapeutic, the decision was taken to use a single classification for all the interventions selected. In the future, the need to adjust this classification for some specific type of operation and how this may be done will be addressed.

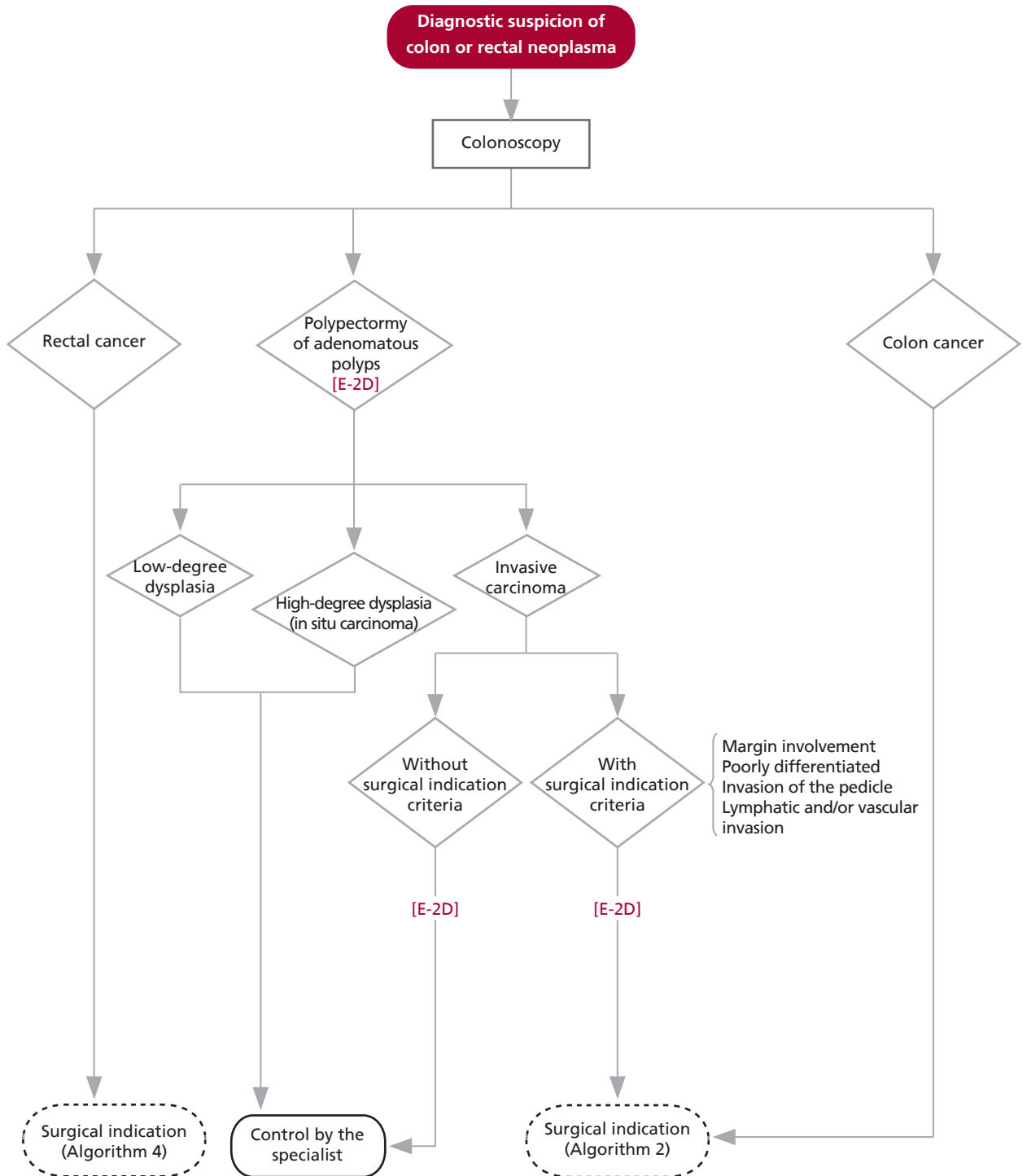
SOURCES OF INFORMATION CONSULTED

- Fédération Nationale des Centres de Lutte Contre le Cancer (www.fnclcc.fr/)
- Institute for Clinical Systems Improvement ICSI (www.icsi.org)
- National Cancer Institute NCI (www.cancer.gov/cancerinfo/pdq/)
- National Comprehensive Cancer Network NCCN (www.nccn.org/)
- National Health Service NHS Scotland (www.show.scot.nhs.uk/sign/guidelines)
- National Institute for Clinical Excellence NICE (www.nice.org.uk/)

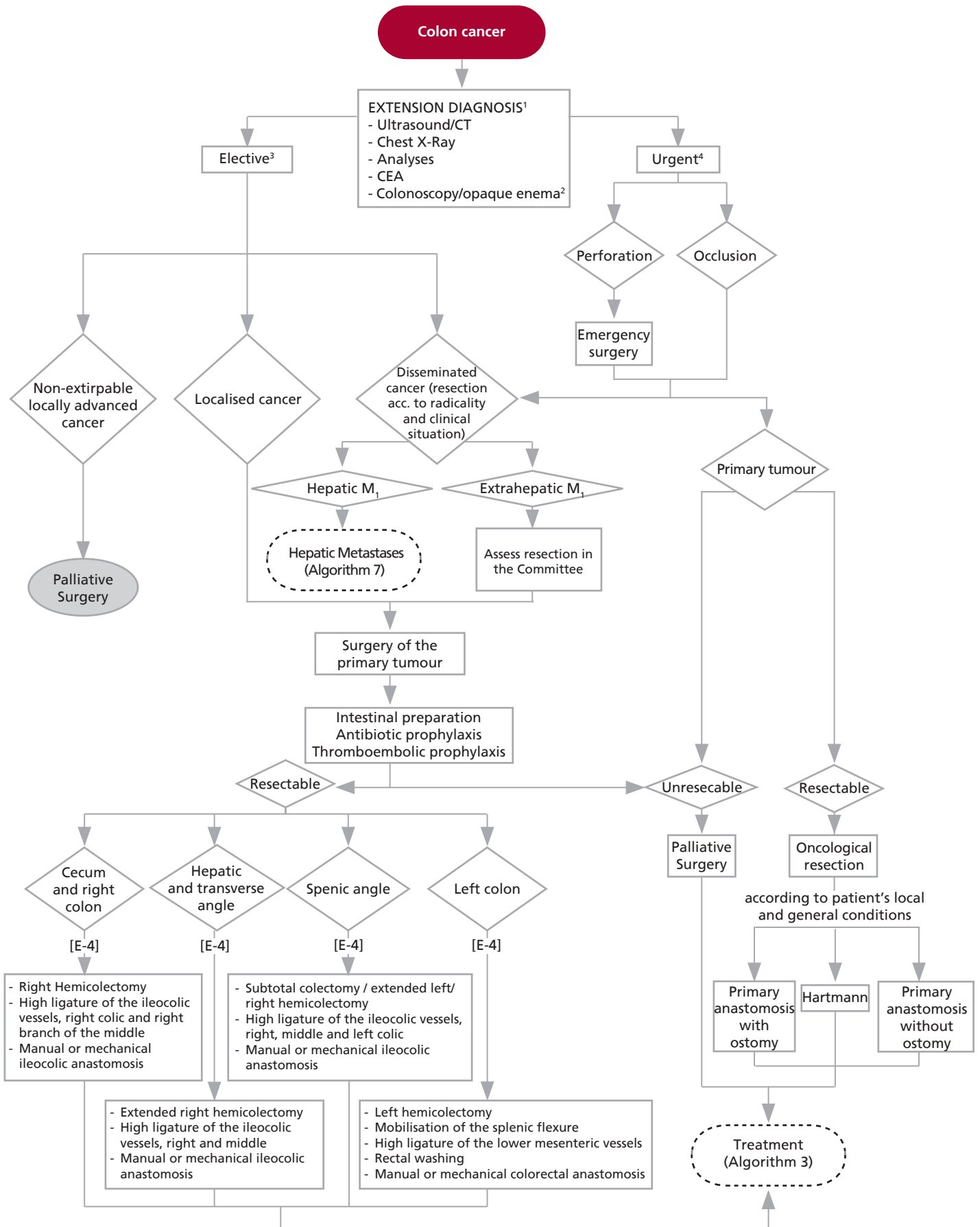
PART II. COLON AND RECTAL ONCOLOGY

ALGORITHMS

ALGORITHM 1. Management of preneoplastic and neoplastic lesions



ALGORITHM 2. Surgical indication of colon cancer

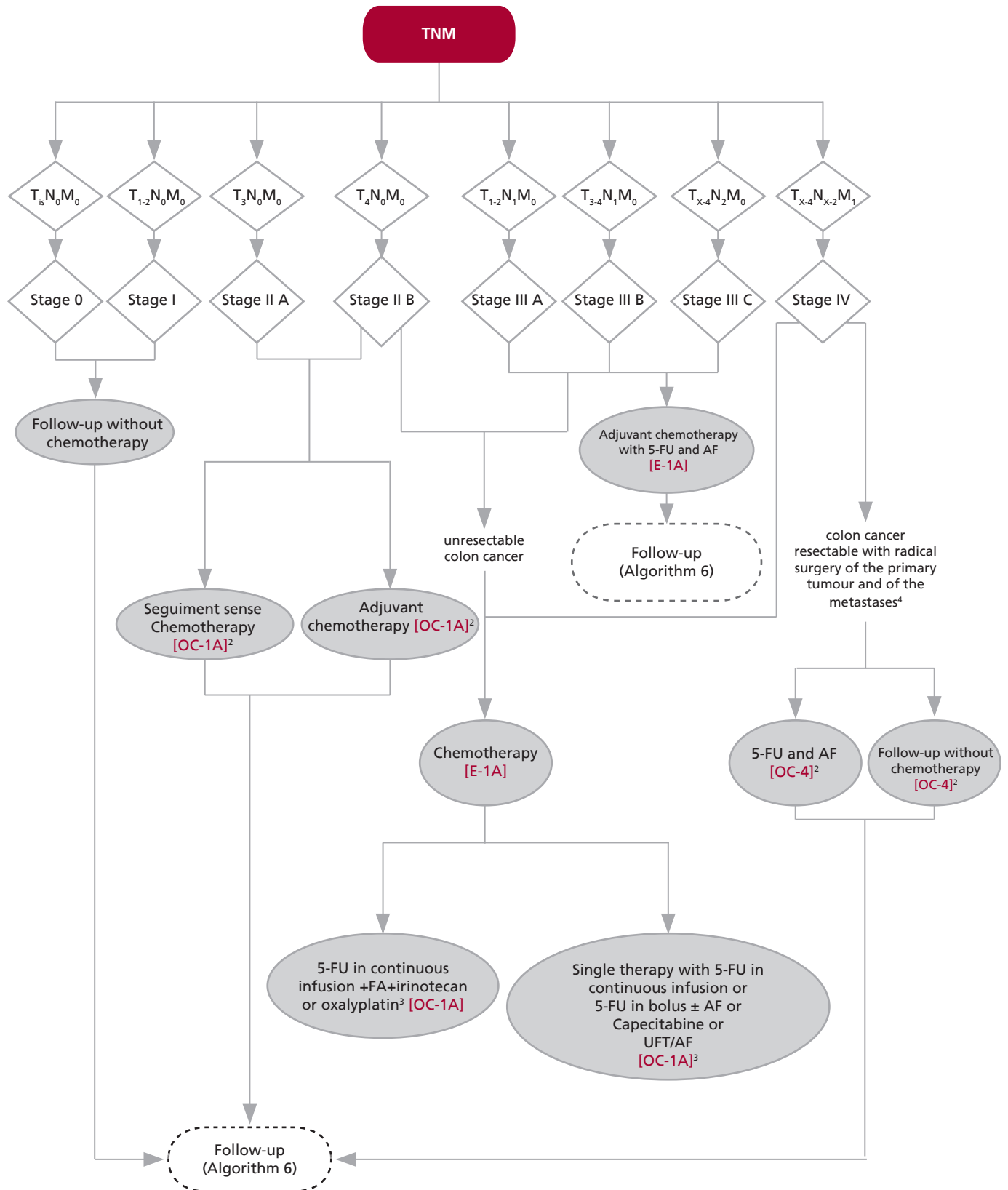


1 Conduct the tests pre-operatively whenever possible; if impossible, complete them post-operatively

2 If the colonoscopy is not complete perform opaque enema
3 See laparoscopy text

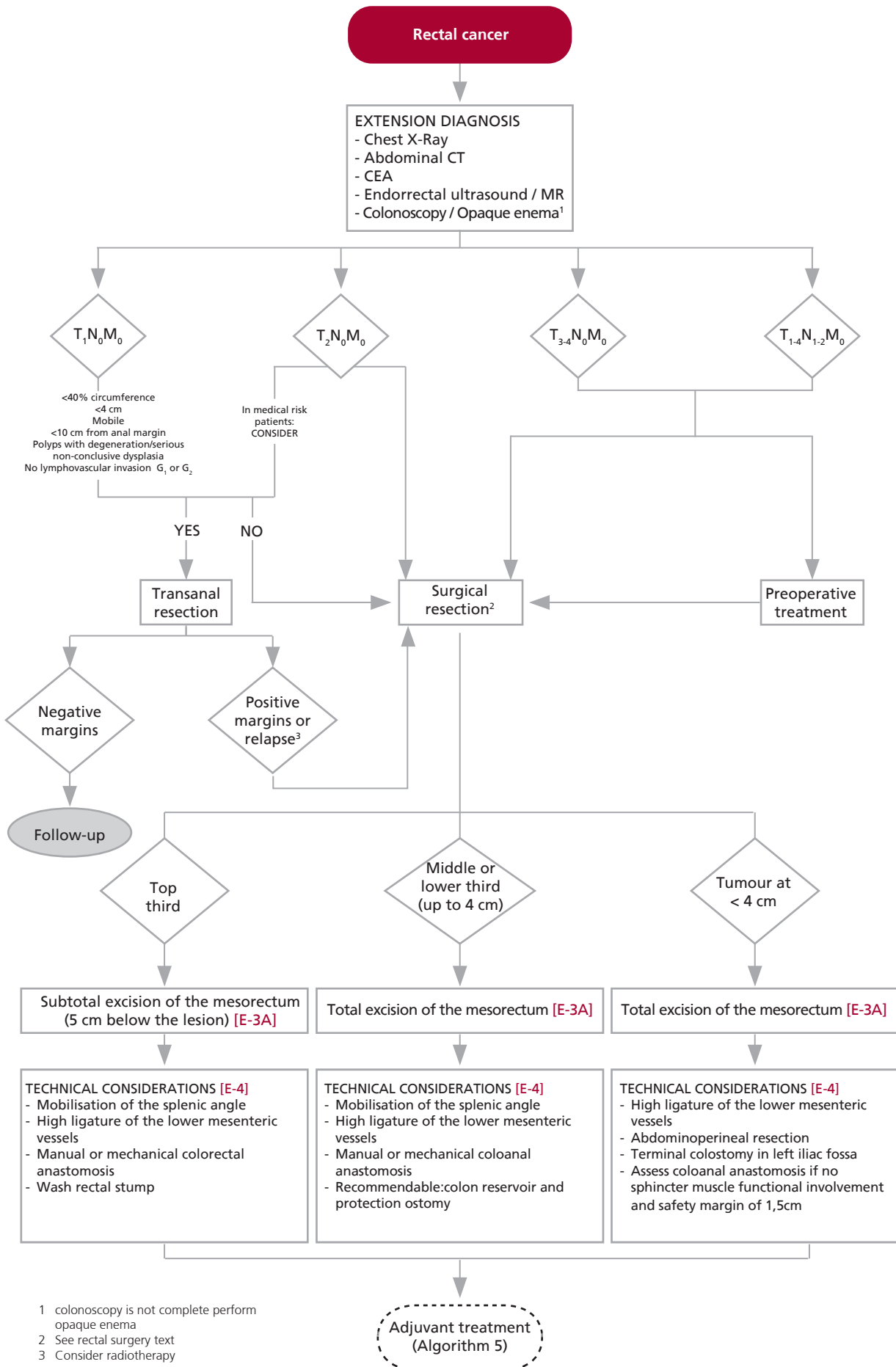
4 See emergency surgery text

Algorithm 3. Complementary treatment of colon cancer by stages¹

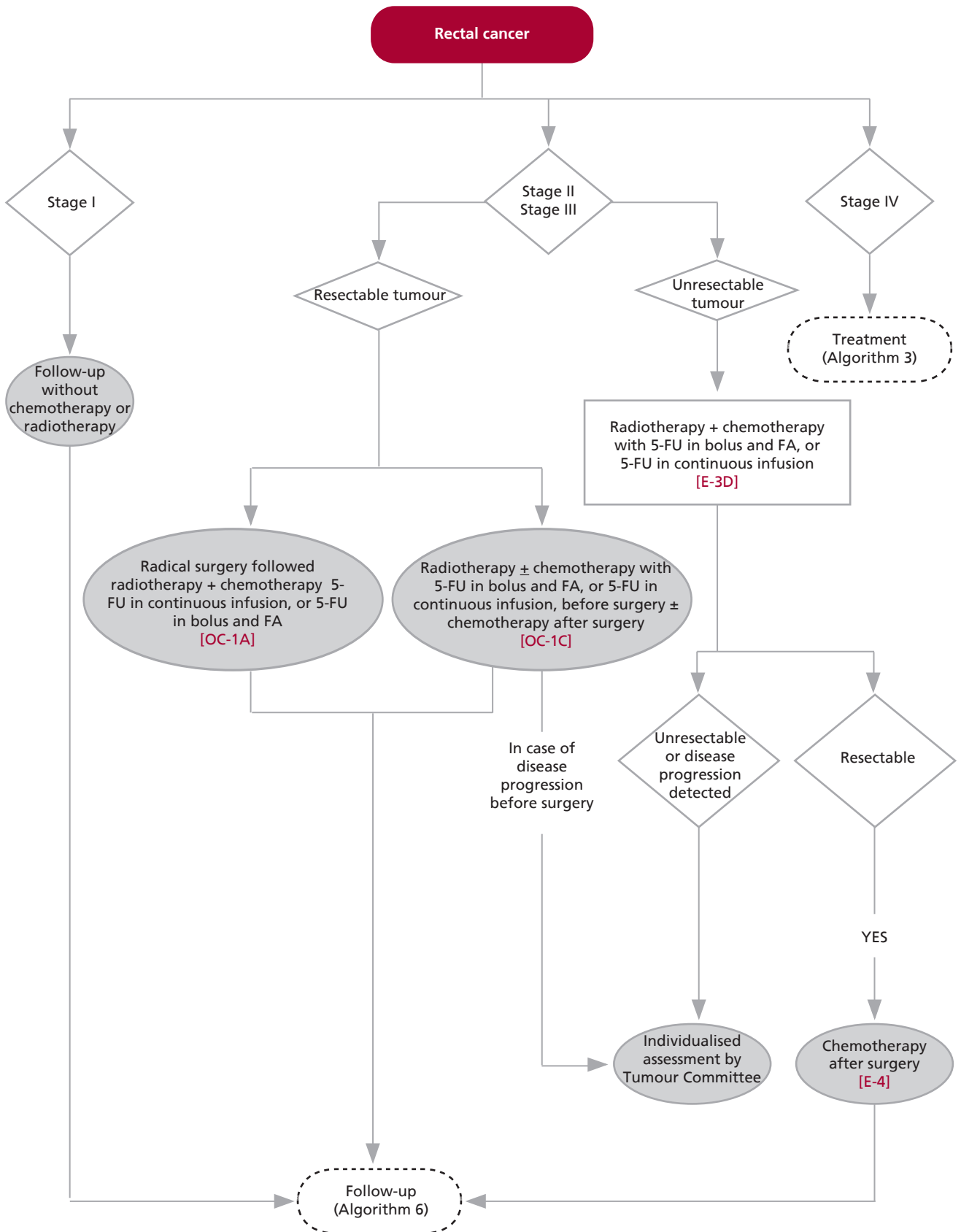


1 See colon cancer chemotherapy text
 2 Consider clinical trial
 3 Consider radiotherapy in case of fixed structures
 4 See Algorithm 7

Algorithm 4. Surgical indication for rectal cancer

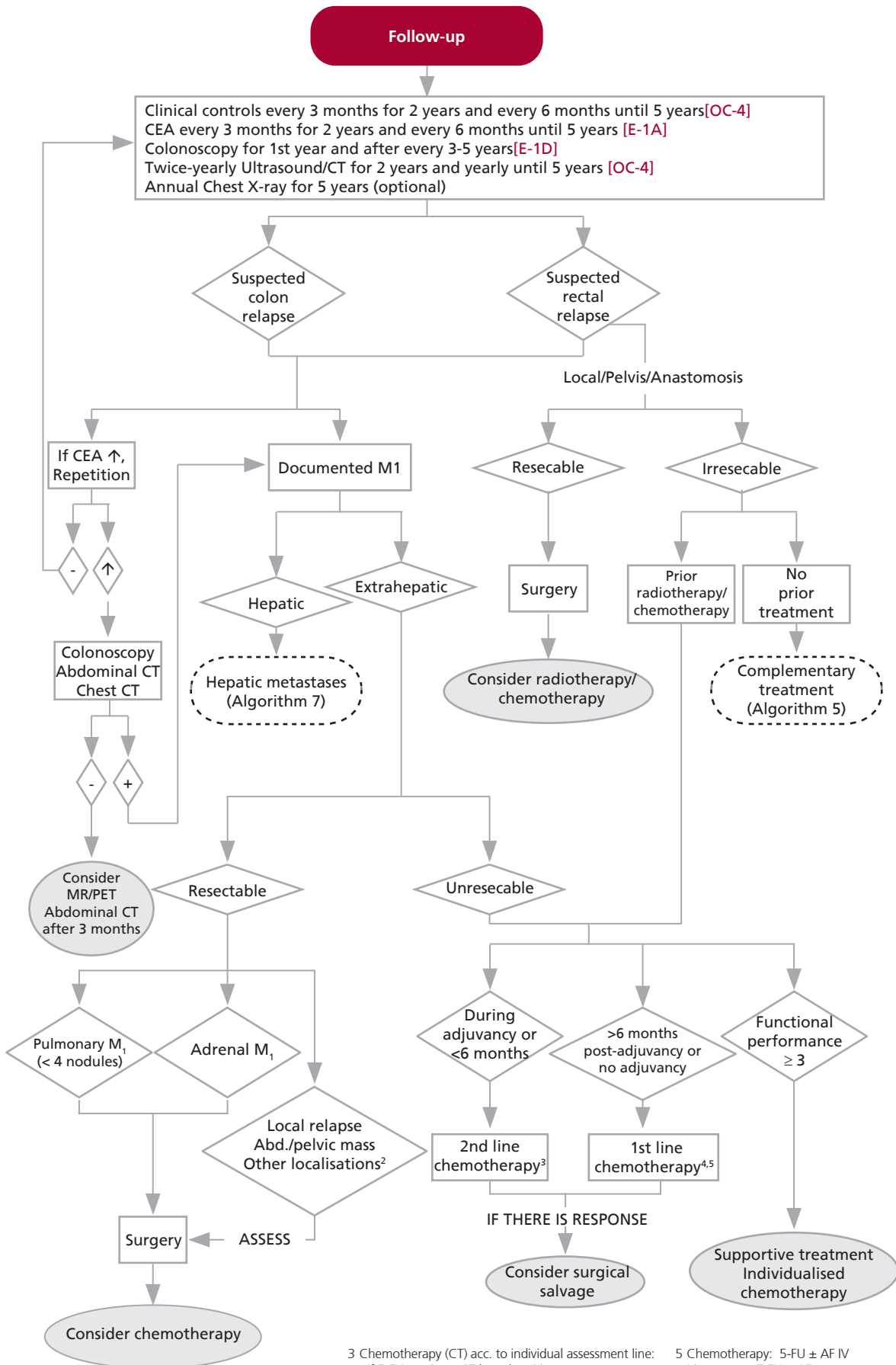


Algorithm 5. Complementary treatment of rectal cancer¹



1 See text

Algorithm 6. Follow-up of local resected disease

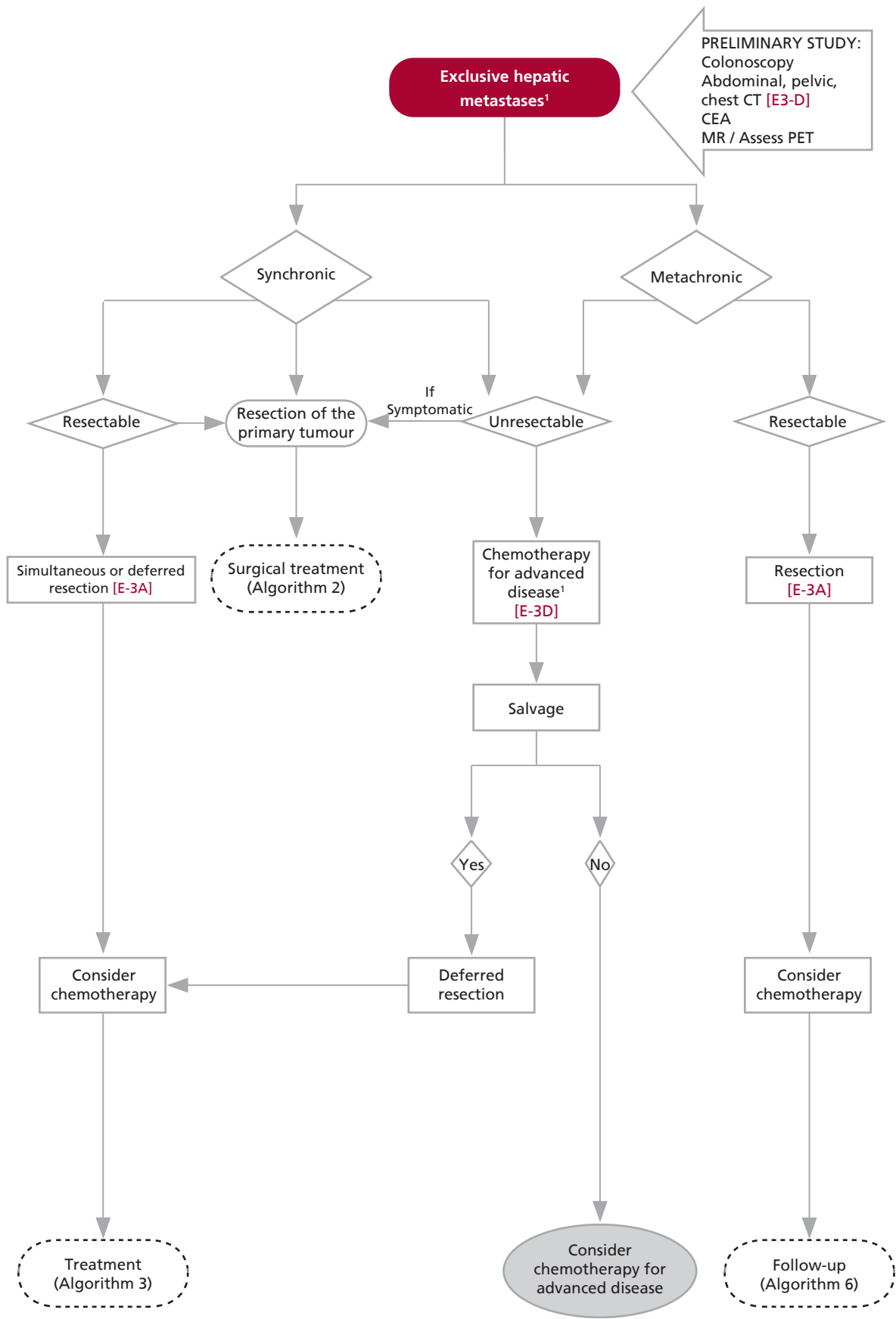


1 If the preoperative colonoscopy is incomplete, perform within the first three months post-surgery
 2 Consider radiotherapy in the event of fixed structures

3 Chemotherapy (CT) acc. to individual assessment line:
 - If 5-FU previous: CT based on irinotecan
 CT based on oxalyplatin
 -If prior irinotecan: CT based on oxalyplatin
 -If prior oxalyplatin: CT based on irinotecan
 4 See text

5 Chemotherapy: 5-FU ± AF IV
 Irinotecan + 5-FU ± AF
 Oxalyplatin + 5-FU ± AF

Algorithm 7. Potentially resectable hepatic metastases



1 See text

INTRODUCTION AND EPIDEMIOLOGY

Colorectal cancer is the second most frequently diagnosed malignant neoplasm in Catalonia, as well as the second cause of death by malignant neoplasm. In our setting, colorectal cancer holds the third place in men and the second in women, and accounts for 14.6% and 15.2%, respectively, of all malignant tumours. According to the data of the Cancer Register of Tarragona, the adjusted incidence of colon cancer is 22 new cases and 19.8 new cases in men and women, respectively, per 100,000 inhabitants and year; and rectal cancer is 12.7 and 6.7 new cases in men and women, respectively, per 100,000 inhabitants and year. According to these same sources, colon cancer accounts for 60% and 70% of all cases of colorectal cancer in men and women, respectively; and rectal cancer for 40% in men and 30% in women. The mean age of the incidence of colon cancer is 68 years in men and 70 years in women; and for rectal cancer it is 69 for men and 70

for women.¹ Rectal tumours are regarded as those whose distal end is located less than 12 centimetres from the anal ring by endoscopy, unless the tumour is above the peritoneal flexion in surgery.^{2,3}

When colon cancer presents as a localised disease in the intestine, it has a high healing rate (50%) with radical surgical treatment. Relapsing disease after radical resection surgery is the most serious problem, causing death in most patients. The prognosis of colon cancer is determined mainly by the degree of penetration of the tumour in the colon wall and by whether or not there is involvement of the regional lymph nodes, with these two factors forming the basis for staging classifications (see Table and Annex). Other adverse prognosis factors are the presence of intestinal perforation and/or obstruction and high preoperative levels of carcinoembryonic antigen (CEA). Other prognosis factors have been evaluated, such

Table. TNM Classification (UICC, 2002)

T CATEGORY (PRIMARY TUMOUR)	
Tx	↔ The primary tumour cannot be assessed
T0	↔ There is no evidence of primary tumour
Tis	↔ <i>In situ</i> intraepithelial carcinoma or invasion of the lamina propria ^a
T1	↔ Tumour that invades the submucosa
T2	↔ Tumour that invades the muscular layer
T3	↔ Tumour that invades the subserosa or the non-peritonealised pericolic or perirectal tissues through the muscular layer
T4	↔ Tumour that directly invades other organs or structures ^{b,c} and/or perforates the visceral peritoneum
CATEGORY N (REGIONAL LYMPH NODES)	
Nx	↔ The regional nodes cannot be assessed
N0	↔ Without regional nodular metastases
N1	↔ Metastases in 1 to 3 regional lymph nodes
N2	↔ Metastases in 4 or more regional lymph nodes
<i>Note:</i> a tumour node in the pericolic / perirectal adipose tissue without histological evidence of lymph node in the nodule is classified in the pN category as metastasis in regional lymph node if the nodule has form and the smooth outline of a lymph node. If the nodule has an irregular outline in should be in the T category and also codes as V1 (microscopic venous invasion) or V2 if it is enormously evident, since there is a high probability that it represents a venous invasion.	
M CATEGORY (METASTASES)	
Mx	↔ The presence of distance metastasis cannot be assessed
M0	↔ No distance metastases are detected
M1	↔ Distance metastasis
GROUPING BY STAGES	
0	Tis N0 M0
I	T1-2 N0 M0
IIA	T3 N0 M0
IIB	T4 N0 M0
IIIA	T1-2 N1 M0
IIIB	T3-4 N1 M0
IIIC	Any T N2 M0
IV	Any T Any N M1

a This includes carcinogenic cells confined in the glandular (intraepithelial) baseline membrane or lamina propria (intramucosa) without extension through the muscularis mucosa to the submucosa.

b Direct invasion in T4 includes invasion of other segments of the colon or rectum through the serosa; for example, invasion of the sigmoid colon by a cecum carcinoma.

c The tumour that adheres to other organs or structures, macroscopically, is classified as T4. However, if there is no tumour present in the adherence, microscopically, the classification should be pT3.

as the allelic loss of the chromosome 18q or the expression of the thymidylate synthase enzyme, although they have not been validated in prospective studies. The instability of microsatellites has been associated with a higher survival in patients with colorectal cancer.

Rectal cancer, when it presents as a localised disease, has a high healing rate (45%) with radical surgical treatment. The prognosis of rectal is mainly determined by the degree of tumour penetration in the rectum wall and by whether or not there is involvement of the regional lymph nodes, with these two factors providing the basis for staging classifications (see Table and Annex). In rectal cancer, the greater limitation of surgical radicality is determined by the presence of the osseous pelvis, which often renders it impossible to

achieve broad surgical margins. Relapse of the disease, both locally and at distance level, after radical resection surgery, is the most serious problem, and is the cause of death in most patients.

There are population groups with a higher incidence of colorectal cancer. These risk groups include patients with hereditary conditions, such as familial adenomatous polyposis, hereditary colorectal cancer not associated with polyposis and the ulcerative colitis. These situations account for 5% of colorectal tumours. Other risk situations for the development of colorectal cancer are personal background of adenomas or colorectal cancer, family history of first degree of colorectal adenoma or cancer or personal history of breast, ovary or endometrium cancer. These patients should be referred to a specific genetic counselling unit.

POLYPECTOMY

Endoscopic polypectomy is the treatment of choice for patients with colorectal adenomas. cohort studies have demonstrated that this measure reduces the incidence of colorectal cancer, which makes it the best preventive strategy [2D] and is why the task force defines it as the standard measure.

In most cases (adenomas low and high degree dysplasia), endoscopic polypectomy is sufficient. However, when the anatomopathological study demonstrates the presence of invasive carcinoma (involvement of the submucosa), it is usually necessary

to conduct a surgical resection since up to 20% of these patients present extension of the disease beyond the resection margins (in more profound planes or regional lymph nodes). Even so, if there coexist different factors with good prognosis (confirmation that the polypectomy is complete, disease-free resection margin of more than 2 mm, well or moderately differentiated carcinoma and the absence of vascular or lymphatic invasion), endoscopic treatment must be regarded as sufficient [2D], and the task force deems it standard.⁴⁻⁵

APPROACH ROUTE IN ELECTIVE COLON SURGERY

The surgical treatment of colon cancer can be performed by open or laparoscopy-assisted surgery. While it was introduced more recently, there is evidence that laparoscopic surgery is associated with a reduction in postoperative morbidity, in analgesic requirements in the immediate postoperative period and in the length of hospital stay. Furthermore, there is a prospective, controlled and randomised study at one centre in non-metastatic patients

which suggests a better prognosis in terms of survival and relapses in patients operated on by laparoscopic surgery. Even so, the confirmation of this surgical option as the treatment of choice requires the validation of results by ongoing multicentre studies. These facts indicate that the laparoscopic approach is a valid alternative for the treatment of colon cancer in expert groups.⁶⁻⁷

EMERGENCY COLON CANCER SURGERY

Colon and rectal carcinoma is the most frequent cause of occlusion of the large intestine. 15-20% of colon tumours initially present in this form. Neoplastic occlusion affects the left colon more frequently; carcinomas of the splenic flexure present an occlusion incidence of 50%. Most patients with occlusive large intestine carcinoma are elderly, and the incidence of occlusion seems to increase with age.

The perforation associated with colon and rectal carcinoma is less frequent than occlusion, and occurs with an incidence of the 2.6–6.5%. Cecal perforation by distension due to distal stenosis of the colon has been described between 1.7% and 18%, with a mortality rate of 50%.

Contrary to what occurs with the management of urgent left colon condition, which is still a matter for debate, different authors agree that right hemicolectomy or right hemicolectomy extended with primary anastomosis is the treatment of choice in occlu-

sive lesions and perforations of the right or transverse colon. On the other hand, there are different alternatives for the treatment of occlusion of the left colon, as treatment in three times, Hartmann's operation, resection with preoperative antegrade washing and primary anastomosis, subtotal colectomy and the placement of an expandable endoluminal prosthesis.⁸⁻¹² There are many arguments in favour of one-off surgery, but this is not always possible, either due to patient characteristics or for technical reasons.

The placement of an endoprosthesis that makes it possible to prepare the colon once the occlusive condition has been addressed appears as a possible and suitable alternative that requires coordination between endoscopist and surgeon. Since there are no conclusive results at the moment, the different options are regarded as suitable and it will be the surgeon, supported by the endoscopist, who will establish the most appropriate technique according to patient characteristics and the experience of the team.

CHEMOTHERAPY IN COLON CANCER

Stages 0 and I. The task force defines that follow-up without adjuvant chemotherapy is the standard treatment.

Stage II.¹³⁻¹⁵ The task force cannot define a standard strategy clearly, and different alternatives are given by way of consensus options. With adjuvant chemotherapy, the results of the clinical tests performed do not agree, since some have shown a benefit with regard to overall and disease-free survival, whereas others have not confirmed this. In any event, the indirect support of documented benefits in patients in stage III [1A]. The most evaluated regimen is the combination of 5-fluorouracil (5-FU) with folinic acid (FA). Some authors recommend adjuvant treatment only in the presence of factors associated with a worse prognosis (adherence or invasion of other organs, resected mesenteric implants, complete or almost complete perforation).

Stage III.¹⁶⁻¹⁸ The task force defines that adjuvant chemotherapy with 5-FU + FA is the

standard treatment. In controlled clinical trials, an improvement in overall survival has been documented with adjuvant chemotherapy [1A]. The 5-FU + FA regimens are the most evaluated ones [1A]. The regimens of 5-FU + FA lasting 6-8 months are at least as efficacious as longer treatments with the combination of 5-FU and levamisol [1A], and adding levamisol to the combination does not improve the results [1A].¹⁹

Stage IV. Resectable liver disease.

The task force cannot define a standard strategy clearly, and different alternatives are given by way of consensus options. Only one randomised test (single-centre) comparing the combination of hepatic intra-arterial chemotherapy with fluorodesoxyuridine and systemic chemotherapy with 5-FU and FA versus exclusive systemic chemotherapy in patients with hepatic metastasis after resection surgery is available.²⁰ The test documented favourable results for the combination with regard to the disease-free and overall survival after 2 years, but not in the survival average.

With these results, and with no further studies available, doing exclusively follow-up is regarded as an option. However, in view of the risk of relapse in patients undergoing radical metastasis surgery (higher in stages III), the administration of systemic adjuvant chemotherapy with the combination of 5-FU and FA may be considered.

In some series of cases, it has been documented that in patients with exclusive hepatic metastases initially deemed unresectable it is possible to achieve resectability in a relevant proportion of cases with chemotherapy [3D].

Stage IV. Unresectable disease.²¹⁻³³ The task force defines the following consensus options: chemotherapy combined with 5-FU + FA + irinotecan or 5-FU + FA + oxalyplatin, and single therapy with fluoropyrimidines (5-FU in continuous infusion ± FA or capecitabine or uracil-tegafur -UFT- + AF).

An improvement of survival in comparison with supportive treatment [1A] has been documented with meta-analyses of clinical

trials with 5-FU-based chemotherapy; controlled clinical trials have documented greater progression-free survival when AF is added to the treatment [1D] and a better overall survival when 5-FU is used in continuous infusion instead of bolus administration [1A]. Controlled clinical trials have obtained similar results with regard to survival when capecitabine or oral UFTs were used instead of i.v. 5-FU. [1A].

In controlled clinical trials it has been documented that regimens combining 5-FU and FA with irinotecan or oxalyplatin as first-line treatment offer a better response rate [1D] and overall survival rate [1A] than treatment with 5-FU and FA, but with a greater incidence of undesired effects.

The data available on raltitrexed demonstrate that its efficacy is equal to or lower than regimens of 5-FU ± FA and therefore its use should be reserved for patients who have contraindications for fluoropyrimidines.³⁴⁻³⁶

RECTAL SURGERY

In rectal tumours, total or subtotal exeresis of the mesorectum is always regarded as obligatory.³⁷⁻⁴¹ The mesorectum is an anatomic and functional unit of the rectum. It corresponds to a well defined structure that harbours a priority lymphatic territory in rectal neoplasms, together with the mesenteric territory as far as the root of the lower mesenteric artery. In rectal neoplasms of the top third, extirpation may be conducted subtotally (respecting the more distal portion of the mesorectum), although some authors recommend treatment of this proximal localisation, at mesorectal level, with the total extirpation of the mesorectum, as in all rectal neoplasms. Extirpation will be performed mainly by avascular planes and with technical security. Anastomoses must be conducted without any degree of tension, which in most cases obligates the release and descent of the splenic angle of the colon. In coloanal anastomoses the conduct of a colon reservoir is addressed. A

protection stoma of low colorectal anastomoses is advisable, and is deemed obligatory when this anastomosis is performed after a programme of preoperative chemotherapy +radiotherapy. The most recommended option is the ileostomy. With total exeresis of the mesorectum, locoregional relapses of rectal neoplasms have fallen from 30% to 5-8% and the five-year survival rate is between 45-50%. Tumour of the circumferential and/or distal mesorectal margin is a very important independent factor as a cause of locoregional relapse and survival.

There are different studies on the impact of the surgeon on the results of colon and rectal cancer surgery in terms of local relapse and long-term survival.⁴²⁻⁴⁵ Different authors demonstrate that both surgeons and the surgical team or centre with a high volume of operated rectal cancer cases are significantly related to a better five-year survival and a lower incidence of local relapses [3A].⁴⁶⁻⁴⁹

CHEMOTHERAPY AND RADIOTHERAPY IN RECTAL CANCER

Stage I. The task force defines that follow-up without adjuvant chemotherapy-radiotherapy is the standard treatment.

Stages II-III.⁵⁰⁻⁷⁶ The task force defines that the combination of radiotherapy and chemotherapy as adjuvant strategy is a standard treatment. Controlled clinical trials have documented that adjuvant radiotherapy reduces local relapses [1D] and that the combination of radiotherapy and chemotherapy improves overall survival [1A]. Regimens of continuous infusion 5-FU during radiotherapy offers better results than bolus administration in terms of relapses and overall survival [1A]. While it is not clear whether adding FA to 5-FU in bolus improves results, it is indirectly supported by the tests performed in colon cancer and the results of ongoing trials are awaited.¹⁹

The task force defines that the combination of radiotherapy and chemotherapy, and the radiotherapy alone as a neoadjuvant strategy before surgery, is a consensus option. In non-controlled clinical trials, it has been documented that the use of radiotherapy alone or in combination with chemotherapy before surgery, in patients with tumours of the lower third permits sphincter preservation in a clinically relevant proportion of patients [3C] without an apparent increase in pelvic relapses [3D]. Preliminary data from controlled clinical trials have documented that the

combination of preoperative chemotherapy with radiotherapy makes it possible to increase sphincter preservation options comparably with initial surgery. On the other hand, non-controlled studies have also documented that combined treatment frequently renders it possible to operate on tumours regarded as unresectable [3D].

As for radiotherapy alone, controlled clinical trials have documented that in resectable tumours, preoperative radiotherapy compared to surgery alone improves local control and reduces rectal cancer mortality, although the surgery used is not regarded as standard nowadays. Although the rate of surgery complications increases and the risk of metastatic disease is not reduced, there is a benefit, albeit small, in survival. There is evidence that radiotherapy administered preoperatively might improve local control as compared to postoperative, but the regimen evaluated is not regarded as standard in our setting and has not been assessed in combination with chemotherapy.

Clinical trials are ongoing aimed at clarifying which strategy, preoperative or postoperative, is best in these stages.

Stage IV. See the recommendations and the synthesis of the evidence corresponding to colon cancer.

POSTOPERATIVE MONITORING IN RADICAL RESECTION NON-METASTATIC COLON AND RECTAL CANCER

At the moment, it is universally accepted that the systematic monitoring of patients with sporadic non-metastatic colon and rectal cancer after a radical operation favours the early detection of neoplastic relapses and of metachronic lesions in an initial treatment-susceptible stage, and increases survival [1A].⁷⁷⁻⁸⁰ However, the most suitable follow-up strategy is unknown, both with regard to the explorations that should be included as well as frequency.^{36,81} In these patients, the expert group of the American Society of Clinical Oncology consid-

ers that there is sufficient evidence to recommend monitoring of the CEA serum levels every 2-3 months for a period of 2 years or more after the operation [1A], as well as a colonoscopy in the first year and then every 3-5 years to detect metachronic lesions [1D]. On the other hand, and while there is not enough data for a recommendation, the task force defines the conduct of clinical controls (anamnesis and physical exploration) and abdominal imaging tests every 3-6 months over the first 3 years and every year until five years as a consensus option. Finally, there is sufficient information not to recom-

mend the periodic conduct of hepatic function tests or haemogram, chest radiography, or the determination of hidden blood in stools.⁸² These explorations are regarded as optional. Patients that belong to certain group risks,

such as hereditary non-polyposis colorectal cancer, familial adenomatous polyposis or inflammatory intestinal disease, among others, may benefit from more intense colonoscopy-based monitoring strategies.

DISSEMINATED COLON CANCER. RESECTION OF HEPATIC METASTASES OF COLORECTAL CARCINOMA

Survival rates after 5 years of 25% to 40% are obtained with the surgical resection of hepatic metastases of colorectal cancer in screened patients, whereas survival is less than 2% without treatment.⁸³⁻⁸⁸ Before proceeding to surgery of hepatic metastasis it is indispensable:

- 1) To be sure that the primary tumour is controlled.
- 2) To conduct a diagnosis of intrahepatic extension.
- 3) To exclude extrahepatic disease.

Staging of patients diagnosed with hepatic metastasis

- 1) To be sure that the primary tumour is controlled a colonoscopy should be performed (unless one has already been done in the last six months). An abdominal and pelvic helical computerised tomography (CT) is recommended. A periodical follow-up of the CEA is also convenient.
- 2) To make a hepatic extension diagnosis (Number of nodules, diameter, relationship with the vascular structure), the most sensitive, specific and cost-effective exploration is the two-phase helical CT (portal and equilibrium).⁸⁹ MR is very useful in patients with hepatic steatosis and allergy to iodised contrast.⁹⁰
- 3) A chest CT must be conducted to exclude extrahepatic disease.⁹¹

Conditions for indicating surgery

Regardless of the prognosis factors of hepatic metastases, the conditions required to indicate surgery of hepatic metastases are:

- Operability of the patient in the absence of contraindications for major surgery.

- Global expectations of mortality in hepatic surgery by hepatic metastases lower than 5%.

- Conditions of resectability:
 - . Possibility of exeresis with free margin of the hepatic and extrahepatic disease, including synchronically or deferred.
 - . Maintenance of sufficient viable hepatic parenchyma.

Prognosis factors of the hepatic metastases

- 1) Good prognosis factors: absence of extrahepatic disease; Under 4 hepatic metastases located in a single lobe localisation far from the vascular structures (portal vein and vena cava); and a diameter of less than 10 cm.^{87,92-94}
- 2) Worst prognosis indications: 4 or more hepatic metastases; bilobular disease; hepatic metastases synchronic with the diagnosis of the primary tumour; presence of resectable extrahepatic disease; tumour diameter greater than 10 cm; and proximity to vascular structures that prevent resection with a healthy parenchymal margin greater than 1 cm.

Intervention with patients with hepatic metastases of colon and rectal cancer

A. Synchronic hepatic metastases: if they are known when the colorectal cancer is diagnosed, a staging must be performed. If they are resectable, if the hospital has the necessary infrastructure and experience and the patient's general condition permitting, simultaneous surgery of the primary tumour and of the hepatic metastases can be performed. An equally valid option is to

perform surgery of the primary tumour, conduct an exploration with biopsy of the hepatic metastases during the operation and deferred surgery of the hepatic metastases 6 weeks later. If the hepatic metastases are a surgical finding and they seem to be resectable at the time, the procedure will be the same: oncological surgery of the primary tumour and intraoperative hepatic exploration with biopsy. Surgery of hepatic metastases without a proper preoperative staging and without the necessary means and experience is contraindicated.

B. Metachronic hepatic metastases (see algorithm 7): are those discovered during follow-up. The procedure will be staging and, if they are resectable, hepatectomy in a centre with the necessary means and experience. If they are unresectable after the staging because they present widespread extrahepatic disease, the patient will be evaluated for treatment with palliative chemotherapy. If there are no extrahepatic metastases, neoadjuvant chemotherapy may salvage between 14% and 50% of previously unresectable patients.⁹⁵⁻⁹⁶

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ANNEX. GENERAL RECOMMENDATIONS FOR THE WRITING OF A REPORT ON THE EXAMINATION OF SURGICAL PARTS WITH COLON AND RECTAL CARCINOMAS

Macroscopic description

1. Specimen sent
 - a) Surgical part
 - b) Dimensions
2. Tumour
 - a) Anatomical localisation
 - b) Configuration
 - Exophytic (pedunculated or sessile)
 - Endophytic (ulcerative)
 - Diffusely infiltrative (linitis plastica)
 - Annular
 - c) Size (three dimensions)
 - d) Ulceration / perforation (no / yes)
 - e) Macroscopic level of invasion
 - Mucosa
 - Submucosa
 - Muscularis propria
 - Subserosa/mesentery
 - Serosa
 - Adjacent structures
- f) Distance from the margins
 - Proximal
 - Distal
 - Radial (margin of the mesorectum)
3. Other non-tumour related lesions
4. Regional lymph nodes
5. Non-regional lymph nodes
6. Appearance of the mucosa not affected by tumour

Microscopic description

1. Histological type (see notes)
2. Histological degree
 - Low degree: $\geq 50\%$ of gland formation (includes well and moderately differentiated)
 - High degree: $< 50\%$ of gland formation (includes poorly and undifferentiated)
3. Extension of the tumour invasion
 - Mucosa (intraepithelial carcinoma or invasion of the lamina propria or muscularis mucosa)
 - Submucosa
 - Muscularis propria
 - Subserosa, mesentery or perirectal adipose tissue
 - Adjacent structures or perforation of the visceral peritoneum
4. Perineural invasion: (no / yes)
5. Vascular invasion of small calibre vessels (angiolymphatic): (no / yes)
6. Venous vascular invasion (no / yes) – it is necessary to specify if it is an invasion of the extramural vessels (see notes)
7. Peritumoral lymphatic response: (non/mild/marked)
8. Growth standard of the tumour periphery
 - Predominantly expansive
 - Predominantly infiltrating
9. Surgical margins (the R classification which indicates the existence of residual postsurgery tumour can be used)
 - The surgical margins cannot be evaluated (Rx)
 - All the margins are tumour-free (R0). Distance to the most proximal margin
 - The tumour affects the margin (the margin must be specified)
 - microscopically (R1)
 - macroscopically (R2)

10. Regional lymph nodes

- Total number of nodes / Number of metastatic nodes

11. Non-regional lymph nodes (the localisation must be specified)

12. pTNM classification (see notes)

13. Degree of regression of rectal carcinomas post-treatment with chemotherapy and/or radiotherapy

Use of the following classification to evaluate treatment-induced tumour regression is recommended:

- GR1 No carcinoma is found
- GR2 Some isolated residual neoplastic cells/glands
- GR3 Predominance of fibrosis on the tumour
- GR4 Partial regression with predominance of tumour on fibrosis
- GR5 Tumour without changes

Diagnosis

It will include, at least, the description of:

- Type of specimen
- Type and histological degree of the tumour
- Staging
- Topographical and morphological SNOMED codes

Explanatory notes

Sampling of the tumour

The samples will be taken at the tumour's maximum penetration point (a minimum of 3 capsules; 5 sections of the tumour should be taken). Samples will also be taken from the transition area between the tumour and non-tumour wall, as well as from the visceral peritoneum of the tumour area.

Histological type: WHO classification (SNOMED code)

- Adenocarcinoma (M8140/3)
- Mucinous adenocarcinoma (colloid) (mucinous component representing >50% of the tumour) (M8480/3)
- Signet ring cell carcinoma (>50% of the tumour) (M8490/3)
- Squamous carcinoma (M8070/3)
- Adeno-squamous carcinoma (M8560/3)
- Small-cell carcinoma (M8041/3)
- Medullary carcinoma (M8510/3)
- Undifferentiated carcinoma (M8020/3)

The existence of total or partial neuroendocrine differentiation will be recorded in the diagnosis

Histological degree

The four-degree adenocarcinoma classification may be used depending on the proportion of glands:

- Degree 1: well differentiated (>95% of the tumour constituted by glands)
- Degree 2: moderately differentiated (50% to 95% of the tumour constituted by glands)
- Degree 3: barely differentiated (5% to 49% of the tumour constituted by glands)
- Degree 4: undifferentiated (<5% of the tumour constituted by glands)

Stratification in only two degrees is recommended (low and high degree). This grouping has been checked to make sure it is more reproducible and reduces intraobserver variations of interpretation. It also has greater value as a prognosis variable. Signet ring cell and small-cell carcinomas are regarded as high degree. Medullary carcinoma is not graduated.

Invasion of venous vessels

The invasion of extramural venous vessels is known to be a negative prognosis factor.

Carcinoma in an adenomatous polyp

If carcinoma is found in a previously resected polyp, the subsequent therapeutic approach will depend on the following factors: Level of invasion, histological degree, distance to the margin and presence of vascular invasion.

- If the carcinoma is limited to the mucosa without passing the muscularis mucosa and the margins are free, there is no need for further action as these lesions are unable to form metastases.
- If the carcinoma invades the submucosa (malignant polyp), the therapeutic approach will depend on:
 - Histological degree of the carcinoma
 - Distance to the margin of resection
 - Vascular invasion

If it is a high-degree tumour, the distance is less than 1 mm and/or there is vascular invasion, segmented surgical resection will be required.

TNM staging system

- pTNM (without treatment before surgery)
- ypTNM (with neoadjuvant chemotherapy or radiotherapy treatment before surgery)

Primary tumour

- Tx The primary tumour cannot be evaluated
- T0 There is no evidence of primary tumour
- Tis Intraepithelial or intramucous tumour without passing the muscularis mucosa
- T1 Tumour that invades the submucosa
- T2 Tumour that invades the muscularis propria

T3 Tumour that crosses the muscularis propria and invades the subserosa or the non-peritoneum coated pericolic or perirectal tissues

T3a+b in an extension <5mm

T3c+d in an extension >5mm

T4 Tumour that invades adjacent structure (T4a) or perforates the visceral peritoneum (T4b)

Besides checking the direct involvement of the visceral peritoneum, peritoneal involvement (pT4b) will also be regarded as when there is inflammatory and/or hyperplastic mesothelial reaction is found with tumour very close to the serosa surface, even if there is no direct involvement.

Regional lymph nodes

Nx Regional lymph nodes cannot be evaluated (nodes < 12)

N0 Regional lymph node metastases are not demonstrated

N1 Metastases in 1 to 3 regional lymph nodes

N2 Metastases in 4 or more regional lymph nodes

The non regional lymph nodes are classified as metastases (pM1). The localisation of these nodes must be specified apart.

Distance metastases

Mx Distance metastases cannot be evaluated

M0 No evidence of distance metastases

M1 Evidence of distance metastases

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