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Is there a place for Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in the treatment of pancreatic adenocarcinoma?

A systematic review.

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Contents

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ABSTRACT

Background

Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) have been introduced in the past three decades in a variety of peritoneal carcinomatosis pathologies. Pseudomyxoma peritonei was historically the first absolute indication for CRS and HIPEC. Nowadays, peritoneal carcinomatosis of colorectal origin has been added to the list of indications for selected patients, while pathologies as of ovarian and gastric origin are under clinical trial evaluation. The use of CRS and HIPEC with good results in other pathologies, such as mesothelioma, appendiceal adenocarcinoma has also been reported in the literature.

Pancreatic adenocarcinoma remains one of the deadliest cancers worldwide, and has a poor, five-year survival rate of 5 %. Due to the lack of early symptoms, the tendency of pancreatic adenocarcinoma to invade adjacent structures or to metastasize and the absence of screening tests available to detect pancreatic cancer in its early stages, many patients with pancreatic cancer already have advanced disease at the time of their diagnosis with a high mortality rate. Although complete surgical resection is the only potentially curative treatment for pancreatic cancer, less than 20 % of newly-diagnosed patients undergo surgical resection with a curative intent. It is important to mention that surgical resection is only considered in patients with completely resectable or borderline-resectable tumors.

In addition, several other therapies for the management of pancreatic cancer have been proposed. However, none of them has been so far established as the treatment of choice, while new therapies emerge. In this respect, pancreatic adenocarcinoma has also been treated with CRS and HIPEC. However, scarce and controversial results are reported.

Aim

The aims of this study are:

a. To describe and present CRS and HIPEC treatment technology.

b. To conduct a systematic review regarding the CRS and HIPEC treatment results for pancreatic adenocarcinoma.

Materials and methods

Medline, Scopus, and international clinical trial registries has been used to acquire information about CRS and HIPEC. Additionally, the systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The following MeSH terms and text words were implied in the search strategy: Group A terms: “CRS” OR “cytoreductive surgery” OR “cytoreduction” OR “Hipec” OR “Hyperthermic Intraperitoneal Chemotherapy”; Group B terms: “pancreas” OR “pancreatic”; Limits were applied to restrict

manuscripts to those related to human subjects;; Group A and group B terms were combined, and limits were applied to the resulting search output.

The description and presentation of CRS and HIPEC treatment technology is presented within the theoretical background of this thesis.

Results

The systematic review revealed 9 manuscripts that met the criteria. In total, 68 cases of pancreatic adenocarcinoma were treated with CRS/HIPEC, after duplicate cases were removed. Thirty-three cases received CRS/HIPEC as an adjuvant for resectable disease with no peritoneal involvement, while the rest 35 cases had peritoneal carcinomatosis of pancreatic adenocarcinoma origin. There were limited data regarding demographic information, HIPEC protocol, open or closed technique, and disease specific survival data. Most of the cases included in the systematic review were presented along with other peritoneal malignancies. Data on survival are very limited and range from 2 to 70 months. Comprehensive data analysis and interpretation are presented in two meaningful Tables created (See Tables 17 and 18).

Conclusions - Research output

There are limited data regarding CRS/HIPEC treatment of pancreatic adenocarcinoma. CRS/HIPEC has been both used as a treatment for peritoneal carcinomatosis of pancreatic origin, and as a preventive approach in resectable pancreatic adenocarcinoma. Even if the application of CRS/HIPEC seems a reasonable approach, the extremely limited data available prevent to draw any safe conclusions; however, it seems that further investigation is required in order to clarify the benefit.

ΠΕΡΙΛΗΨΗ

Η κυτταρομειωτική Χειρουργική (CRS) και η Υπέρθερμη Ενδοπεριτοναϊκή Χημειοθεραπεία (HIPEC) χρησιμοποιήθηκαν την τελευταία τριακονταετία σε ένα ευρύ φάσμα νοσημάτων περιτοναϊκής καρκινωμάτωσης. Ιστορικά, το ψευδομύξωμα περιτοναίου απετέλεσε την πρώτη απόλυτη ένδειξη για CRS / HIPEC. Σήμερα, στις ενδείξεις σε επιλεγμένους ασθενείς έχει προστεθεί η καρκινωμάτωση του περιτοναίου από εντεροκολικό καρκίνο ενώ η χρήση CRS / HIPEC σε περιτοναϊκές μεταστάσεις που προέρχονται από γαστρικό καρκίνο ή καρκίνο των ωοθηκών αποτελούν αντικείμενο κλινικής έρευνας. Επίσης έχει αναφερθεί με πολύ ικανοποιητικά αποτελέσματα η χρήση CRS / HIPEC και σε άλλες ιστολογίες, όπως τα πρωτοπαθή νεοπλάσματα του περιτοναίου (κυρίως μεσοθηλίωμα), το αδενοκαρκίνωμα σκωληκοειδούς απόφυσης, κ.α.

Το αδενοκαρκίνωμα το παγκρέατος παραμένει ένας από τους πλέον θανατηφόρους καρκίνους και έχει πενταετή επιβίωση της τάξης του 5%. Λόγω της απουσίας πρώιμης συμπτωματολογίας, της τάσης του αδενοκαρκινώματος να καταλαμβάνει παρακείμενους ιστούς ή να μεθίσταται πρώιμα, μαζί με την έλλειψη διαγνωστικών εξετάσεων ανίχνευσής του σε αρχικά στάδια, έχει σαν αποτέλεσμα οι πάσχοντες να έχουν ήδη προχωρημένη νόσο τη στιγμή που διαγιγνώσκονται και υψηλό ποσοστό θνησιμότητας. Η πλήρης χειρουργική εξαίρεση είναι η μόνη θεραπεία του καρκίνου του παγκρέατος, ωστόσο λιγότερο του 20% των νεοδιαγνωσθέντων ασθενών έχουν ένδειξη χειρουργικής επέμβασης. Θα πρέπει να τονισθεί ότι η χειρουργική αφαίρεση έχει νόημα μόνο σε ασθενείς με πλήρως ή οριακά εξαιρέσιμο καρκίνο του παγκρέατος.

Έχουν προταθεί κατά καιρούς πολλές νέες θεραπείες για την αντιμετώπιση του καρκίνου του παγκρέατος. Ωστόσο μέχρι στιγμής, καμία δεν έχει καθιερωθεί σαν η θεραπεία εκλογής, ενώ παράλληλα προτείνονται και άλλες. Μια τέτοια νέα θεραπευτική προσέγγιση για το αδενοκαρκίνωμα του παγκρέατος αποτελεί ο συνδυασμός της κυτταρομειωτικής χειρουργικής με υπερθερμική ενδοπεριτοναϊκή χημειοθεραπεία. Ωστόσο έχουν αναφερθεί λίγα και αντιφατικά αποτελέσματα για τη χρήση της στους ασθενείς αυτούς.

Για τον λόγο αυτό, ο σκοπός της παρούσας διπλωματικής εργασίας είναι:

a. Να παρουσιάσουμε την τεχνολογία και να περιγράψουμε τις διαδικασίες που εφαρμόζονται στο συνδυασμό της κυτταρομειωτικής Χειρουργικής με την υπερθερμική ενδοπεριτοναϊκή χημειοθεραπεία.

b. Να προβούμε σε μια συστηματική ανασκόπηση της διεθνούς βιβλιογραφίας που αφορά τα αποτελέσματα αυτής της θεραπευτικής μεθόδου σε ασθενείς με αδενοκαρκίνωμα του παγκρέατος.

Η μεθοδολογία που ακολουθήσαμε ήταν:

a. Ανασκόπηση της προσιτής σε εμάς βιβλιογραφίας σχετικά με την τεχνολογία και τις τεχνικές της CRS και HIPEC.

b. Η συστηματική ανασκόπηση έγινε σύμφωνα με το πρωτόκολλο Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Οι ακόλουθοι όροι Mesh και λέξεις χρησιμοποιήθηκαν στην Αγγλική γλώσσα για τη στρατηγική ανεύρεσης: Group A terms: “CRS” OR “cytoreductive surgery” OR “cytoreduction” OR “Hipec” OR “Hyperthermic Intraperitoneal Chemotherapy”. Group B terms: “pancreas” OR “pancreatic”. Χρησιμοποιήθηκαν επιπλέον φίλτρα για τον περιορισμό σε εργασίες που αφορούσαν ανθρώπους, ήταν στην Αγγλική γλώσσα και είχαν δημοσιευθεί την τελευταία δεκαετία. Για την αναζήτηση χρησιμοποιήθηκαν οι βάσεις δεδομένων Medline, Scopus, Cochrane, καθώς και international clinical trial registries. Τέλος συνδυάστηκαν τα ευρήματα των Group A and group B terms και στο αποτέλεσμα εφαρμόσθηκαν τα προαναφερθέντα φίλτρα.

Η τεχνολογία και οι τεχνικές της CRS και HIPEC παρουσιάζονται στο θεωρητικό μέρος αυτής της εργασίας.

Η συστηματική ανασκόπηση της βιβλιογραφίας κατέληξε σε εννέα άρθρα που πληρούσαν τα προκαθορισθέντα κριτήρια. Μετά την αφαίρεση των διπλοαναφορών, βρέθηκαν συνολικά 68 περιπτώσεις παγκρεατικού αδενοκαρκινώματος που έλαβαν θεραπεία με CRS και HIPEC. Από αυτές, σε 33 περιπτώσεις έγινε επικουρικά CRS και HIPEC μετά από αφαιρέσιμη νόσο χωρίς περιτοναϊκή συμμετοχή ενώ οι υπόλοιπες 35 περιπτώσεις ενεφάνιζαν καρκινωμάτωση του περιτοναίου λόγω παγκρεατικού αδενοκαρκινώματος. Και στις 9 εργασίες υπάρχουν περιορισμένα και ελλιπή στοιχεία σ ότι αφορά τα δημογραφικά δεδομένα, το πρωτόκολλο HIPEC που ακολουθήθηκε, και τους ειδικούς για τη νόσο δείκτες επιβίωσης που επετεύχθησαν. Οι περισσότερες περιπτώσεις που συμπεριλαμβάνονται στην παρούσα συστηματική ανασκόπηση, παρουσιάζονται μαζί με άλλης αιτιολογίας καρκινωματώσεις του περιτοναίου. Υπάρχουν εξαιρετικά λίγα δεδομένα για την επιβίωση, που κυμαίνεται από 2-78 μήνες. Συνολικά, τα δεδομένα παρουσιάζονται αναλυτικά στο ειδικό μέρος και συνοπτικά στους Πίνακες 17 και 18.

Συμπερασματικά, με την εργασία αυτή παρέχεται στον αναγνώστη η δυνατότητα ανασκόπησης της σχετικής με το θέμα βιβλιογραφίας και κατανόησης της CRS και HIPEC στη θεραπεία του αδενοκαρκινώματος του παγκρέατος. Ο συνδυασμός CRS και HIPEC έχει χρησιμοποιηθεί τόσο για την αντιμετώπιση περιτοναϊκών μεταστάσεων παγκρεατικής αιτιολογίας όσο και σαν προφυλακτική θεραπεία σε εξαιρέσιμο αδενοκαρκίνωμα του παγκρέατος. Φαίνεται ότι η θεραπευτική αυτή μέθοδος έχει βάση, ωστόσο τα εξαιρετικά λιγοστά βιβλιογραφικά δεδομένα εμποδίζουν την εξαγωγή ασφαλούς συμπεράσματος και απαιτείται περισσότερη έρευνα προκειμένου να τεκμηριωθούν τα πιθανά οφέλη από την εφαρμογή της.

THEORETICAL BACKGROUND (GENERAL SECTION)

1. Introduction on Pancreatic Cancer

1.1. Incidence

There is a strong genetic background in 5 % – 10 % of pancreatic cancers. The main risk factors of pancreatic cancer are smoking and dietary habits (obesity, red meat intake, low vegetables intake, diabetes and alcohol consumption) [1]. Location wise, approximately 60 % – 70 % of pancreatic cancer is in the head of the pancreas, 20 % – 25 % in the body and the tail and the remaining 10 % – 20 % is diffused along the pancreas [1, 2]. Pancreatic cancer arises from both the exocrine and endocrine parts of the gland. However, ~95 % of adenocarcinomas occur within the exocrine portion and may stem from acinar cells, the ductal epithelium, or from connective tissue [1, 3].

1.2. Diagnosis

Tumors of the head usually present with jaundice while other common symptoms include weight loss, abdominal pain, steatorrhoea, and new-onset diabetes. Tumors of the head of pancreas can invade locally into the proximal duodenum while tumors of the body and tail usually grow in the distal duodenum. Both can result in an upper gastroduodenal obstruction [1].

The preferred imaging tool for pancreatic specific imaging is the multi-detector computed tomography (MDCT) angiography using a dual-phase pancreatic protocol, with contrast enhancement during both the pancreatic and the portal venous phases. When contrast-enhanced CT is not feasible (e.g. allergy to iodinated contrast material) or when a suspected lesion is poorly characterized, then MRI is indicated. PET/CT scan might be used in high risk patients in order to detect remote metastases outside the pancreas. In order to facilitate the decision-making process and ensure a thorough assessment of all essential criteria for optimal staging, it is recommended to use a standardized radiology report staging template. After such a high-quality imaging has been performed as described above to evaluate the extent of disease, a multidisciplinary consultation regarding diagnostic management and resectability should take place. [*NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Pancreatic Adenocarcinoma. Version 3.2017. September 11, 2017. Accessed from: https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf*].

In a simplified form, the diagnostic algorithm to evaluate pancreatic cancer is shown in the Figure below:

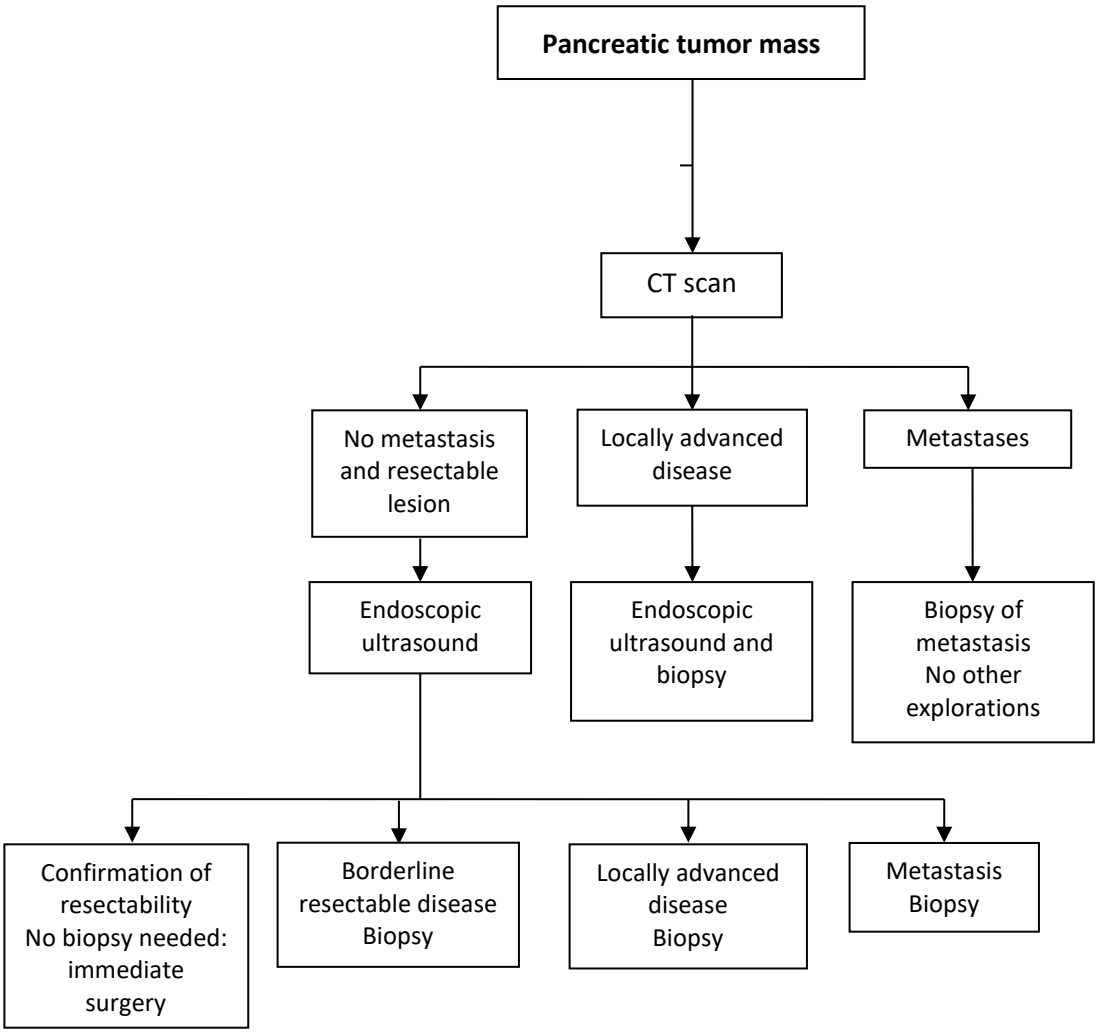

Figure 1. Diagnostic work-up before multidisciplinary decision *(From: ref. #1).*

CT: computed tomography.

1.3. Pathology

The primary purpose of pathologic analysis of the pancreatic specimen is to determine the pathologic stage of the tumor by evaluating the type, grade, size and extent of the cancer. The most common pancreatic cancer is the ductal adenocarcinoma. Microscopically, this neoplasm is presented under various forms: From a well differentiated duct shaped carcinoma giving the impression of a benign gland to a poorly differentiated carcinoma, where the epithelial differentiation can be shown immunologically only. Typically, the ductal adenocarcinoma provokes an intense stromal reaction, which is considered to act as a

chemotherapy barrier [2]. Several morphological variants of ductal carcinoma have been described, including colloid and medullary carcinomas.

It is also important to recognize some other variants of pancreatic cancer which are associated with a poorer prognosis, such as adenosquamous carcinoma and undifferentiated carcinomas with osteoclast-like giant cells. On the contrary, acinar cell pancreatic cancers have a slightly better prognosis [3].

The second most frequent tumors of the pancreas, having a specific pattern, are the neuroendocrine tumors, while cystic neoplasms represent 10 % – 15 % of pancreatic cystic lesions [4]. The most common cystic neoplasms are: Serous cystadenoma, intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (cystadenoma or cystadenocarcinoma). The mucinous lesions may potentially be converted to malignancy or may already harbor a malignancy, in contrast to the non-mucinous lesions which have no malignant potential.

The College of American Pathologists (CAP) has introduced a pathology report template specifically oriented to pancreatic cancer. This includes, apart from the standard TNM staging, some other relevant to the prognosis and the evolution of the disease variables as well. This template is also currently adopted from the NCCN Pancreatic Cancer Panel.

1.4. Staging

Since just a limited number of pancreatic cancer patients are candidates for surgical resection and may undergo chemotherapy regimens it is advisable that a TNM classification must cover both the clinical and the pathological staging.

The following Table presents the TNM classification of pancreatic cancer:

Table 1: TNM classification.

Primary tumor (T)
T0 = No evidence of primary tumor
Tis = Carcinoma *in situ*
T1 = Tumor limited to the pancreas, ≤ 2 cm in greatest dimension
T2 = Tumor limited to the pancreas, > 2 cm in greatest dimension
T3 = Tumor extends beyond the pancreas but without involvement of the celiac axis or the SMA
T4 = Tumor involves the celiac axis or the SMA (unresectable primary tumor)
Regional lymph nodes (N)
NX = Regional lymph nodes cannot be assessed
N0 = No regional lymph node metastasis
N1 = Regional lymph node metastasis
(A minimum number of 10 lymph nodes analyzed are recommended).
The regional lymph nodes are the peripancreatic nodes which may be subdivided as follows:
Superior: Superior to head & body
Inferior: Inferior to head & body
Anterior: Anterior pancreaticoduodenal, pyloric (for tumors of head only), & proximal mesenteric
Posterior: Posterior pancreaticoduodenal, common bile duct, & proximal mesenteric
Celiac : For tumors of head only
Distant metastasis (M)
M0 = No distant metastases
M1 = Distant metastasis

From Ref #1.

Table 2 shows the group staging of pancreatic cancer according to the American Joint Committee on Cancer (AJCC):

Table 2: Stage Grouping according to the American Joint Committee on Cancer (AJCC) TNM Staging of Pancreatic Cancer (2010).

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

However, in everyday clinical practice most centers are using a more practical classification system which is mainly based upon the outcomes of the dedicated radiology imaging as described before: Thus, after staging by pancreatic protocol CT (and sometimes together with ultrasound and/or MRI/MRCP or ERCP), liver function tests & chest imaging, the pancreatic cancer can be classified to the following four categories:

1. Resectable.
2. Borderline resectable (i.e. tumors that are in the twilight zone involving nearby structures to be neither clearly resectable nor clearly unresectable with high chance of an R1 resection).
3. Locally advanced unresectable (i.e. tumors that are involved with nearby structures to such an extent that are unresectable despite the absence of metastatic disease).
4. Disseminated.

1.5. Treatment strategy

The decision regarding diagnostic management and resectability has to be the product of a multidisciplinary consultation after considering both the results of appropriate imaging as well as the clinical status of the patient.

Different treatment modalities reside in the armamentum for the treatment of pancreatic Ca. In brief they are presented in the following Table and they will be discussed in more details below:

Table 3: Current therapies for the management of pancreatic cancer (except CRS & HIPEC)

Therapeutic option	Subset
Surgical resection	Cephalic pancreatoduodenectomy Distal pancreatectomy Total pancreatectomy
Chemotherapy	Neoadjuvant: Gemcitabine Adjuvant: Gemcitabine, 5-Fluorouracil Advanced: Gemcitabine, Gemcitabine + fluropyrimidines, Gemcitabine + platinum analogs, Gemcitabine + erlotinib, FOLFIRINOX, Nab-paclitaxel
Chemo-Radiation therapy	Neoadjuvant: Radiation + 5-fluorouracil, Radiation + paclitaxel, Proton beam radiation + capecitabine. Adjuvant: Radiation + 5-Fluorouracil, Radiation + gemcitabine, Radiation + chemotherapy. Advanced: Radiation + 5-fluorouracil, Radiation + chemotherapy, Stereotactic body radiotherapy
Personalized therapy	Target specific point mutations, Mitomycin C, Immune system stimulation

Modified from Ref #5.

The treatment option depends from the staging of the disease. This can be seen in the tables we created located the Appendix section (Table A1 - Table A9), from the initial workout till the treatment guidelines, according the reciprocal staging. The abbreviations listed regarding levels of evidence and grades of recommendation in each Table can be found in the Appendix. All Tables are modified/copied from the latest *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Pancreatic Adenocarcinoma. Version 3.2017. September 11, 2017. Accessed from: https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf*].

A summary of different treatment options according to staging and level of recommendation can be seen in Table 4.

Table 4: A summary of different treatment options according to staging and level of recommendation.

Treatment of localized disease

- A multidisciplinary team is necessary
- Tumor clearance should be given for all seven margins identified by the surgeon [IV, B]
- Standard lymphadenectomy should involve the removal of ≥ 15 lymph nodes to allow adequate pathologic staging of the disease [IV, A]
- Adjuvant treatment is done with either gemcitabine or 5-FU folinic acid [I, A]
- No chemoradiation should be given to patients after surgery except in clinical trials [I, E]

Treatment of non-resectable disease: borderline resectable lesions

- Patients with borderline resectable lesions should be included in clinical trials wherever possible
- In routine practice, if the patient is not included in a trial, a period of chemotherapy followed by chemoradiation & the surgery appears to be the best option [IV, B]

Treatment of non-resectable disease: locally advanced disease

- The standard of care is 6 months of gemcitabine [I, A]
- A minor role of chemoradiation in this subgroup of patients has been observed [I, A]
- It is impossible to recommend any chemoradiation treatment other than the classical combination of capecitabine & radiotherapy [IV, C]

Treatment of metastatic disease

- Palliative & supportive care: Duodenal obstruction is preferably managed by endoscopic placement of an expandable metal dent when possible, & is favored over surgery [V, B]
- Possible stenting: the endoscopic method is safer than percutaneous insertion & is as successful as surgical hepatojejunostomy [II, B]
- Pain control is mandatory & frequently needs the help of a pain specialist
- For patients with performance status of ¾, with significant morbidities & a very short life expectancy: only symptomatic treatment can be considered
- In very selected patients with Eastern Cooperative Oncology Group (ECOG) status 2, due to heavy tumor load, gemcitabine & nab-paclitaxel can be considered for best chance of response [II, B]
- For patients with performance status of 2 and/or bilirubin level higher than 1.5x upper limit of normal (ULN): a monotherapy with gemcitabine could be considered [I, A]
- If the performance status of the patient is 0 or 1 & the bilirubin level is below 1.5x ULN two types of combination chemotherapy-the FOLFIRINOX regimen or the combination of gemcitabine & nab-paclitaxel-should be considered [I, A]

Personalized medicine

- A few targetable mutations have been identified in pancreatic cancer
- There is no role today for personalized medicine in this cancer [IV, C]

Follow-up & long-term implications

- There is no evidence that regular follow-up after initial therapy with curative intent is useful [IV, D]

1.6. Prognosis

The median survival for resectable disease, after surgical resection of pancreatic cancer ranges from 11-20 months, with a five-year survival from 7-25% [6, 7]. Patients with non-resectable locally advanced disease (Stage III) have a median survival of 6-11 months [8]. Patients who have metastatic disease have a median survival of only 2-6 months [9]. The Table below (Table 5) shows the median survival range as derived from ref #10 and #11.

Table 5: Prognosis of Pancreatic Cancer Patients per Stage: Median Survival (months).

Stage	Median survival (months)
IA	24.1
IB	20.6
IIA	15.4
IIB	12.7
III	10.6
IV	4.5

In summary, resection is the treatment of choice of pancreatic adenocarcinoma and therefore when resectability is feasible, most patients must undergo surgery and adjuvant therapy. In case of borderline resectable disease selected patients with resectable disease can undergo neoadjuvant therapy to increase the chance for an R0 resection. In cases of locally advanced unresectable or metastatic disease, if the patients have an acceptable performance status, they can have chemotherapy and/or chemoradiation with the option of repeating this regimen if a good performance status is maintained after progression. Finally, in patients with disseminated and advanced pancreatic cancer, the only option is to provide specific palliative measures.

2. The Rationale of Cytoreductive Pancreatic Ca surgery (CRS)

The resection of pancreatic carcinoma is the potentially curative treatment option [12, 13, 14, 15]. The overall 5-year survival rate is very poor, up to 10 – 15 % in the best scenario [16, 17, 18], although from specialized high-volume centers it has been reported a survival as high as 20 – 25 % [19, 20].

This stems from the fact that just a small percentage of pancreatic carcinoma patients are diagnosed with early disease at first. This is due to the fact that the disease aggressiveness is very high and occult metastases (usually to local lymph nodes and to the liver parenchyma) are already present when the patient arrives for initial diagnosis. Therefore, the surgical resection is the only regimen left to hopefully provide complete clearance of the malignancy [21].

The resectability criteria according to NCCN Guidelines [*NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Pancreatic Adenocarcinoma. Version 3.2017. September 11, 2017. Accessed from: https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf*] are listed in the Table below:

Table 6: Criteria defining resectability.

Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Solid tumor contact with variant arterial anatomy (ex: accessory or replaced right hepatic artery, replaced CHA and the origin of accessory or replaced artery) and the presence and degree of tumor contact should be noted if present as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure.	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Unresectable	Distant metastasis (including non-regional lymph node metastasis) Head/uncinate process: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° • Solid tumor contact with the first jejunal SMA branch Body and tail • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	Head/uncinate process • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV Body and tail • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

Thus, unfortunately, pancreatic cancer is characterized from its low resectability rate which in the best case is reaches up to 10 – 15 % of the diagnosed tumors [12, 13, 14, 15]. This is due to the fact that at the time of initial diagnosis, a vast majority of these tumors are already unresectable as they already infiltrate major anatomic vessels, and/or even if in some cases local tumors are resectable, they already have distant and unresectable metastases [22].

Today the long-term survival of adenocarcinoma patients after pancreaticoduodenectomy is less than 10 % [23] and the overall 5-year survival rate does not exceed 10 – 15 % [16, 17, 18]. Additionally, a complete resection has a local failure of at least 50 % [24]. The same low prognostic numbers have been reported even in patients with uninvolved lymph nodes: The risk of a local-only recurrence is substantially increased with a serious impairment of the quality of life [25].

The reasons for this failure of surgery are:

1. The anatomical location of pancreas presents already per se a difficulty to provide adequate surgical margins of resection in most patients. Therefore, a “no touch cancer resection” is impossible in most cases as it is unavoidable to traumatize the resected cancer specimen. In most cases the surrounding vital structures and often positive, and the margins of resection are minimal at best. Therefore, patients with pancreatic cancer have an unfavorable prognosis even though R0 resection is possible.

2. Additionally, the primary pancreas lesions have an aggressive tumor biology which leads to early dissemination of the cancer cells into the portal blood and lymphatic channels. This dissemination might be due either to early cancer cells evasion or during or due to tumor dissemination during surgical manipulations [26]. Moreover, if there is a positive margin of resection, it can be assumed that the local recurrence is due to a local progression of small volume residual disease. However, it has been noticed that patients after an R0 resection with clear margins, a local recurrence at the resection site presents. This phenomenon of local recurrence of pancreatic lesions, despite a clear margin of resection is called “**tumor cell entrapment hypothesis**” and three prominent causes have been postulated (see Figure 2).

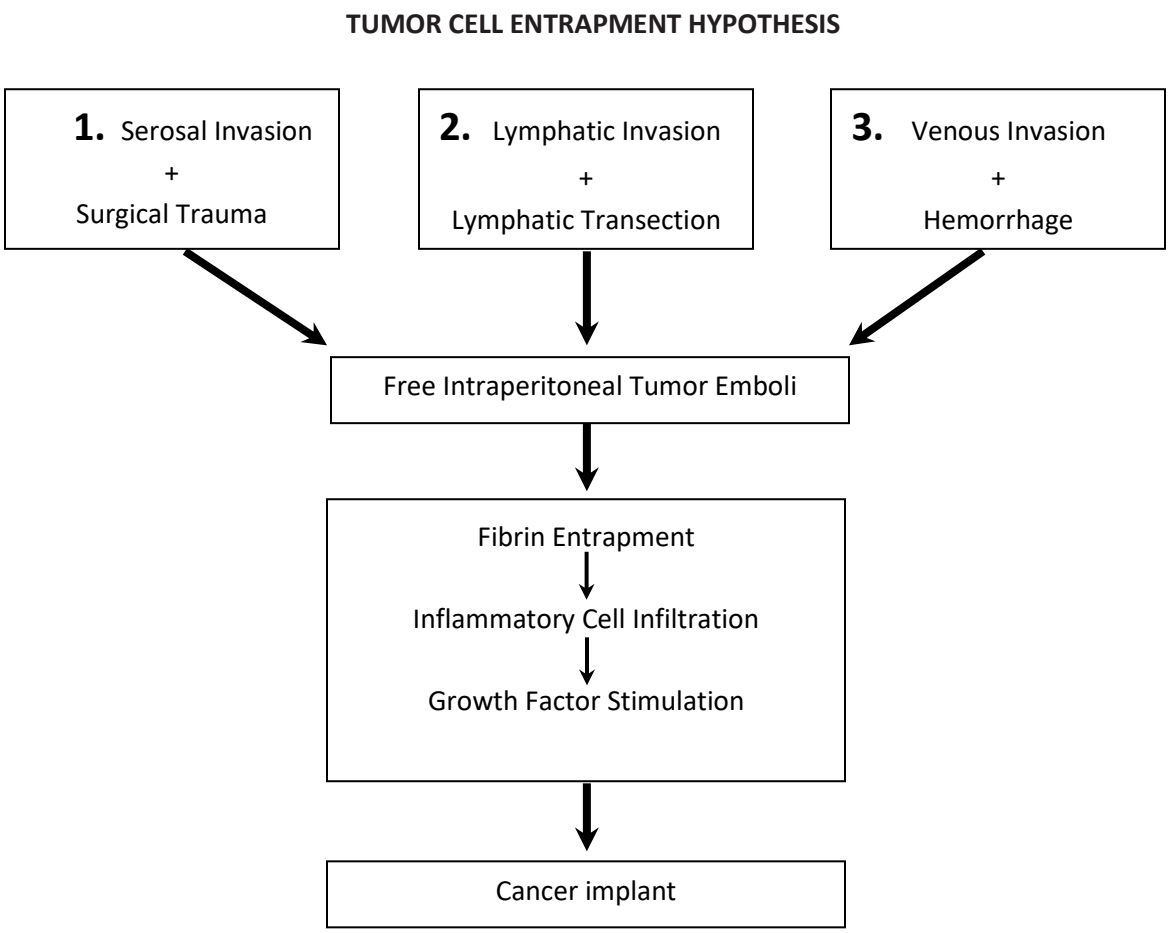

Figure 2. Tumor cell entrapment illustrating pathophysiology of free cancer cells released from the process of pancreaticoduodenectomy *(Modified from Ref #24)*.

The first mechanism of dissemination of the free cancer cells is local serosal implantation at the surgical trauma, leading to the appearance of a local recurrence mass in the site of resection [27]. Additionally, peritoneal implantations (metastases) are also expected to appear as well. Thus, in 50 % or more of patients without initially evident dissemination, during follow-up a local recurrence and/or peritoneal metastases are detected. An explanation for this has been postulated: During surgical resection, some cancer cells escape locally and/or migrate distantly and grow rapidly to either a local recurrence or delivering a distal metastasis. Another alternative explanation is also presented that, presumably, micrometastases are already present in the liver and the lymph nodes, but they were clinically silent. Therefore, a holistic treatment approach after surgery resection in pancreatic cancer patients, must address all of the aforementioned sites of possible metastases [24].

The three different sites of initial treatment failure as well as the percentage of their occurrence probability in resected pancreas cancer patients are shown in Figure 3.

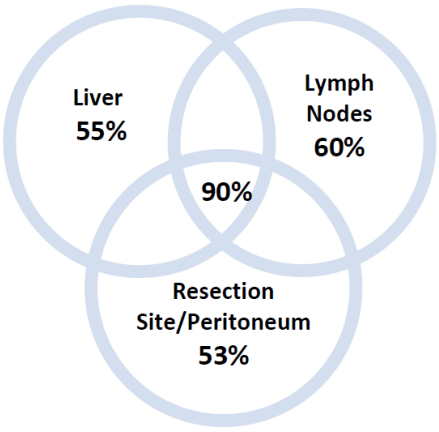

Figure 3. Resected pancreatic cancer: Percentages of initial treatment failure in the different sites. *(Modified from Ref # 24).*

In summary, the problematic anatomic location of the pancreas combined with the aggressiveness of pancreatic tumors have as a consequence a high failure percentage of the regional treatment. Therefore, nowadays the pancreaticoduodenectomy is considered as just a debulking intervention. It is evident that research has a two-fold target in order to increase the long-term survival: a) To device methods to decrease the number of patients with locally unresectable tumors and b) To develop therapeutic regimens capable to control local recurrence.

3. Types of pancreatic surgery intervention

Surgical intervention in pancreatic cancers aims to achieve an R0 resection, although the pancreatic cancer biology usually is prohibitive for this. In any case, the scope of a margin-negative dissection must focus on scrupulous excision of the lesion, identify and assess the need for vascular dissection and/or reconstruction, and to evaluate if an extra pancreatic organ resection is needed. The following types of surgical intervention can be identified:

3.1. Total pancreatectomy

In total pancreatectomy it is imperative to perform a margin negative dissection. If cancer is detected in a margin specimen then a very poor long-term survival can be expected [28]. The following literature is indicative of the published total pancreatectomies for pancreatic cancer:

In one study, total pancreatectomy was performed in 48 patients with pancreatic cancer as routine strategy but without portal vein or superior mesenteric artery resections been part of it. The four-year survival was 21 % [29].

In another study on 150 patients who had pancreatic surgery for cancer, in a selected cases subgroup, total pancreatectomy was recommended hoping to achieve complete remittance. In this subgroup, the operation lasted longer, portal vein resection was more often required, and symptomatic hypoglycemia was more common. Survival data were not available [30].

In a German study, total pancreatectomy was performed in 233 patients, corresponding to the 53.7 % of all pancreas resections which were due to both benign and malignant lesions. The surgical morbidity and mortality was 37.3 % and 7.8 % respectively. Independent variables of hospital mortality were a long operative time, high blood loss, and arterial reconstruction. The cases of pancreatic adenocarcinoma without vascular resection had a median survival of 36.7 months while the 5-year survival rate was of 25.7 %. In contrast, the cases were arterial resection was performed, the median survival dropped to 18.8 months and the 5-year survival rate was diminished to 14.1, ($p<0.001$) [31].

The question on whether, in terms of local control, the total pancreatectomy is superior to the pancreatoduodenectomy (described below) still remains undetermined as it has not been tested due to the unavoidable diabetes after a total pancreatectomy [24].

3.2. Pancreatoduodenectomy (Whipple technique)

During this procedure, the prior complete mobilization of the portal vein (PV) and superior mesenteric vein (SMV) from the uncinate process allows for medial dissection of pancreatic head lesions, assuming of course that there is no evidence of vascular involvement. Dissection laterally, posteriorly and anteriorly of the superior mesenteric artery (SMA) down to the level of the vascular adventitia optimizes the uncinate process mobilization and oncological margin [32, 33].

If the preoperative imaging doesn't reveal frank venous occlusion, then in order to achieve an R0 resection, a lateral venorrhaphy or complete PV or SMV resection and reconstruction could be considered, although this is commonly not revealed before the pancreatic neck has been cut. It is worthwhile to note that quite often the carcinoma is tethered to the lateral wall of the PV so a meticulous mobilization of the vein away from the pancreas is required. This might not be feasible in all cases since the vein wall may present tumor infiltration-related desmoplasia. When tumor infiltration of the vein is suspected, a radical partial or complete vessel resection has been suggested by some authors [33]. Further evidence is obviously needed before this approach is universally accepted and meanwhile a judicious use of this technique appears to be reasonable in selected cases.

3.3. Distal Pancreatectomy

As in pancreatoduodenectomy, the goal of left-sided resection is identical. However, there are much more obstacles to successfully those goals. All these obstacles are related to the frequently advanced stage at diagnosis. It must be mentioned that spleen sparing surgery is not the case for adenocarcinoma. More than that, a R0 resection for distal pancreatic adenocarcinoma, additionally requires an en bloc organ beyond the spleen removal in up to 40 % of the cases [34, 35].

Additionally, in distal pancreatectomy if complete tumor clearance can be achieved, vein excision and reconstruction or lateral venorrhaphy, as well as dissection up to the celiac axis and SMA adventitia has to be considered like during pancreatoduodenectomy [36].

3.4. Extended lymphadenectomy

To improve the pancreaticoduodenectomy outcomes, surgeons thought that a more thorough en bloc lymph nodes resection apart those included in the standard pancreaticoduodenectomy would result in a better outcome.

Thus, additional resection of most normal appearing lymphatics is suggested from above to below the pancreatectomy site including celiac trunk nodes, along the common hepatic artery nodes, paraortic nodes, and vena cava ones. The rationale behind those extended en bloc resections is that R0 resection is the only independent factor associated with best possible overall survival rates.

However, almost all the published randomized controlled trials (RCTs) that compare standard versus extended lymph node dissection report a worse outcome after extended lymphadenectomy. In more details:

An extended lymphadenectomy group (36 resected lymph nodes) was compared to a 15 resected lymph nodes group. It is important to mention that both the groups underwent adjuvant radiotherapy. There were no differences in 5-year overall survival rates (16.4 % vs. 16.5 %). On the contrary, there was decline in the quality of life for the extended lymph node dissection patients [37].

A study summarized the results of four RCTs and reported that extended lymph node dissection had not better survival rates for pancreatic adenocarcinoma located in the head of the pancreas [38].

In a similar review of controlled data, Pavlidis et al. report that RCTs did not reveal any survival benefit in pancreatic cancer patients [39].

Into the same conclusion arrived a meta-analysis study regarding the efficacy of pancreaticoduodenectomy versus extended lymphadenectomy: There was no survival benefit for the extended lymph node dissection group. On the contrary, authors report increased duration of the procedure and higher rates of postoperative complications [40].

However, there is still a debate regarding the optimal number of lymph nodes resection in pancreatic cancer surgery: A study analyzed 3868 pancreas cancer cases that received lymphadenectomy. Those with zero lymph nodes removed yielded the worst outcome ($p < 0.001$) while those with less than 12 lymph nodes removed had a decreased survival compared to those with 12 or more lymph nodes removed. However, one has to interpret these findings with caution since there are a lot of selection biases in this study [41].

In a more recent study, a better outcome was observed when fewer metastatic lymph nodes and more resected lymph nodes, was the case [42].

4. Current treatment modalities

4.1. Chemotherapy (Adjuvant, Neoadjuvant)

Pancreatic adenocarcinoma must receive systemic chemotherapy in all its stages. However, in all cases, biopsy confirmation of the disease must be obtained before the start of the treatment. If for any reason, some other cancer types are confirmed, then the patient should be treated according to the appropriate NCCN Guidelines. The main chemotherapy regimens used in pancreatic cancer are described below:

Gemcitabine Monotherapy

Gemcitabine is used as monotherapy or in conjunction with other chemotherapy agents. It has been shown that in patients with locally advanced or metastatic disease, gemcitabine monotherapy provides better clinical outcomes and slightly better survival rates over regiment with 5-FU. Furthermore, it is an option for 1st-line treatment for patients with metastases or locally advanced disease with a good performance status. Also, approved gemcitabine indication is the symptomatic treatment. Thus, gemcitabine is indicated for patients with symptoms attributed to the metastatic or locally advanced unresectable disease and poor performance status. Finally, gemcitabine as a monotherapy has evidence that supports adjuvant treatment use [43].

In order to predict the response to gemcitabine, a human equilibrative nucleoside transporter 1 (hENT1) has been studied and preliminary clinical data showed that hENT1 expression may act as a predictive biomarker for response to gemcitabine. Further studies based on hENT1 expression are certainly needed for this very promising biomarker and the research is expected to flourish once commercial source of the antibody will be available and CLIA-approved testing will be available [44].

Gemcitabine Combinations:

Gemcitabine combinations have been used in the treatment of pancreatic cancer. Four combinations of the drug have already been reported:

1. *Gemcitabine Plus Albumin-Bound Paclitaxel*
2. *Gemcitabine Plus Erlotinib and Other Targeted Therapeutics*
3. *Gemcitabine Plus Cisplatin*
4. *Gemcitabine Plus Capecitabine*

Their efficacy is reviewed in two meta-analyses of randomized controlled trials, It is reported that in the advanced setting, gemcitabine combinations offer a marginal benefit in overall survival over gemcitabine monotherapy but in the expense of a significant increase in toxicity [45, 46].

Fluorouracil 5-FU/Leucovorin

Fluorouracil (5-FU) with leucovorin is, per guidelines, a Category 1 option adjuvant treatment. The ESPAC-1 trial concluded that 5-FU with leucovorin is superior when compared to observation alone [47]. Also, the ESPAC-3 trial regarding bolus 5-FU with leucovorin vs. gemcitabine as adjuvant therapy after surgery, revealed no survival differences (23.0 months and 23.6 months, respectively) [48].

FOLFIRINOX

It is a combination therapy which includes 5-FU/leucovorin plus oxaliplatin and irinotecan (FOLFIRINOX). It is suggested for the treatment of patients with metastatic solid tumors. FOLFIRINOX is has received Category 2A recommendation for locally advanced unresectable disease. FOLFIRINOX is an acceptable alternative in the neoadjuvant treatments for borderline resectable pancreatic cancer disease. The patients' quality of life of metrics related with this regimen is maintained and even more improved than when gemcitabine is used [49].

4.2. Radiochemotherapy

Radiochemotherapy has been used as an adjuvant to surgical resection. It consists of a concurrent radiation burst together with chemotherapy administration of gemcitabine or fluoropyrimidine. The theory behind this combined approach, lies into the fact that chemotherapy acts as a radiosensitizer and increases the cell toxicity of radiation: In other words, it is suggested that chemotherapy decreases the number of tumor cells which are in S phase of the cell cycle, at which they are more resistant to the radiation damage.

Radiochemotherapy is reported in pancreatic cancer patients both preoperatively as well as postoperatively to the resection site [50].

However, several variables have to be taken into account regarding the proper time for applying this regimen:

Theoretically, the administration of preoperative radiochemotherapy has some advantages:

1. Shrinkage of the size of the primary tumor and therefore improved excision margins.
2. Partially devitalizing the malignancy from micrometastases both at the resection as well in the peritoneum.

The disadvantages of preoperative radiochemotherapy are:

1. Postponing surgery after the chemotherapy treatment may aggravate the situation as the patients need to be operated as fast as possible.
2. In case of a biliary tract obstruction, the bile infection can prolong a surgical procedure to relieve the required bile duct obstruction.

The postoperative radiochemotherapy used to be an adjuvant to surgical resection for many years [51] until a randomized study with large numbers of patients showed that the use of postoperative radiation therapy hasn't not improve survival [52].

In summary, plenty of studies failed to prove any advantage favoring radiochemotherapy for pancreatic cancer either preoperatively or postoperatively [53] and none of them was able to show that this regimen can be established as a treatment choice [54], although sporadically the local-regional control of the disease was increased. However, neither the quality of life nor the long-term survival haven't improved by this costly treatment.

Another alternative radiation therapy method was used in pancreatic cancer: Some authors have studied the application of intraoperative radiation therapy (IORT) aiming to improve survival rate or better local control of the disease: One study showed that IORT treated patients show a decreased incidence of local-regional progression, but without any survival benefit [55]. Other investigators have tried to apply IORT in the adjuvant setting for resectable pancreatic adenocarcinoma but failed to show any promising outcomes [56, 57].

4.3. Hyperthermic intraperitoneal chemotherapy (HIPEC)

HIPEC has been lately used for pancreatic adenocarcinoma treatment, based on the rationale that very high drug intraperitoneal (IP) concentrations can be achieved limiting systemic toxicity.

Today, the term HIPEC refers not only to IP chemotherapy therapy but to the concomitant cytoreductive surgery which precedes as well.

The rationale for HIPEC stems from the advantages attributed to the intraperitoneal therapy, i.e. a) the very high drug concentrations achieved in contact with floating tumor cells and with the lining surfaces at-risk, b) the limited drug absorption. In this way, a significant drug exposure of the tumor is achieved with a very limited systemic toxicity [60]. Only HIPEC, or IP administration, can achieve such high drug concentrations in vivo [58].

Pharmacologic data shows that about 90 % of intraperitoneal chemotherapy is cleared from the peritoneum through absorption by the visceral part of it (and then cleared though the portal vein to the liver) as well as through the visceral subperitoneal lymph (and then from lymph nodes to the thoracic duct). This is in great contrast with the inability of parietal peritoneum to absorb the chemotherapy, thus resulting in high levels of chemotherapy accumulation into the peritoneum [24].

Since tumors recurrence is quite rapid, it seems justified to apply the intraperitoneal (IP) chemotherapy right at the end of cytoreductive surgery in the operating room [59].

Since the duration of chemotherapy intraperitoneal administration is inherently limited, other factors such as hyperthermia have been used to synergistically increase the intensity of the therapy, in terms of cytotoxicity. The theory behind for the use of hyperthermia stemmed from

adequate laboratory evidence that found that heat may present a synergistic action with certain chemotherapeutic agents. It has also been shown that tumor cells are more sensitive to heat than the normal ones, as heat makes the membrane of the cancer cells more permeable, thus allowing more chemotherapy to enter [59].

Typically, HIPEC is infused between 41 ^{0}C and 43 ^{0}C. Above 43 ^{0}C, a harm from the perfusion has been noticed which was attributed to heat-related necrosis. Empirically, the window between 41 ^{0}C up to 43 ^{0}C has been proven to be safe in clinical practice without any side effects from the use of hyperthermia has been reported, except some temporary rise in core temperature, usually in the range of 37.5 ^{0}C to 39 ^{0}C, which reverts rapidly to normal upon termination of the perfusion. However, in order to avoid increased core temperature, several preventing measures are applied, such as stopping applying heat to fluids or skin surfaces, application of cold blankets and cold IV fluids.

Although theoretically, the effect of adding hyperthermia could be extremely easy to study clinically (for instance a randomized trial of chemotherapy infusion at 37 ^{0}C vs 42 ^{0}C), no such study has been performed so far. Thus, the advantage of increasing hyperthermia, while theoretically it is quite plausible, remains questionable [60].

Another benefit of HIPEC is the limited systemic uptake of intraperitoneal chemotherapy, thus avoiding in the early postoperative period some major systemic toxicities related to chemotherapy, such as neutropenia or thrombocytopenia. However, some variable degree of bone marrow suppression has been reported in some series involving CRS + HIPEC, but in early clinical trials, just a few patients showed grade IV marrow suppression. This was in great contrast when systemic drugs were used instead, which provoked systemic side effects [60].

Two variations of HIPEC application technique exist: The open and the closed ones.

1. The open (Coliseum) technique.

In the open technique, a heater circulator, one heat exchanger, one reservoir, an extracorporeal system of two inflow and two outflow tubes, and four temperature probes are usually used. After placing the tubes and the temperature probes, the skin edges are elevated on the rim of a self-retaining retractor. A plastic sheet is attached to the edges of the abdominal incision which covers the abdomen and prevents splashing or diffusion of the chemotherapy aerosols into the operating room. A slit in the plastic sheet allows the surgeon's hand to access the abdomen and pelvis. The surgeon puts a hand in the belly and by moving it, continually secures that all abdominal surfaces will have access to uniform doses of heat and chemotherapy solution. A prime solution of three liters is instilled prior to the administration of the chemotherapeutic agent. As soon as the mean abdominal temperature exceeds 41 ^{0}C, the cytostatic regimen is administered in the abdominal cavity and pumped in and out via a closed pump perfusion circuit. A smoke evacuator pulls the air which is beneath the plastic sheet through a charcoal filter to prevent any aerosols from gaining access to the operating room environment (Figure 4).

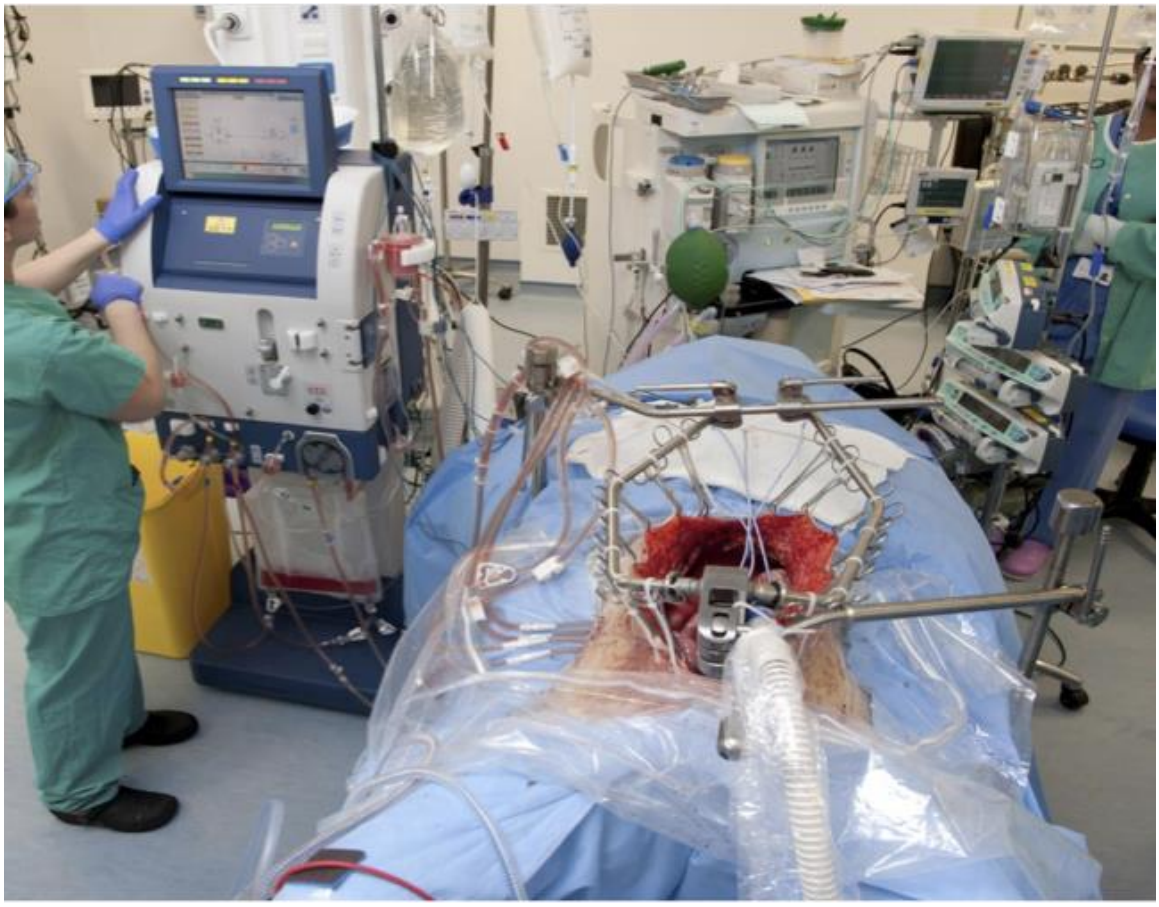

Figure 4. Open heated intraoperative intraperitoneal chemotherapy (HIPEC). *(*Figure colosseum *courtesy of Andreas Larentzakis private collection).*

In cases where administration of IP normothermic chemotherapy is planned, an intraperitoneal port is placed. This is carried out when surgery and HIPEC is complete and just prior to the closure of the abdominal wall [61]. (Figure 5a,b).

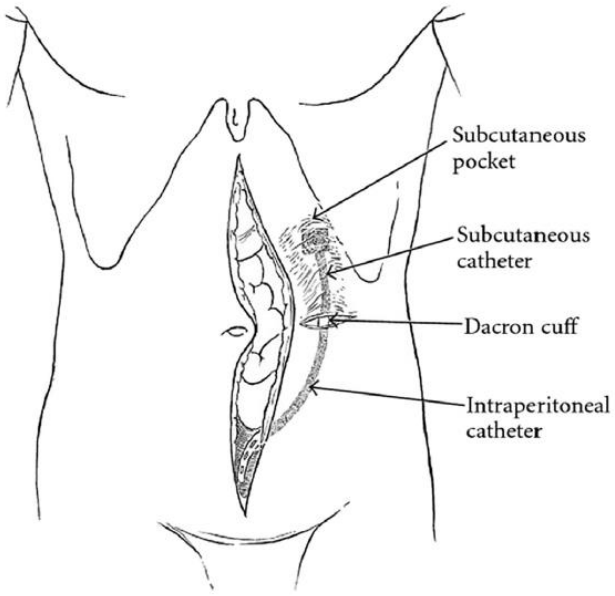

Figure.5a. Preparation to insert an intraperitoneal port at the time of pancreatic duodenectomy.

A lateral skin incision allows dissection of the port pocket and access to the abdomen using a stab incision.

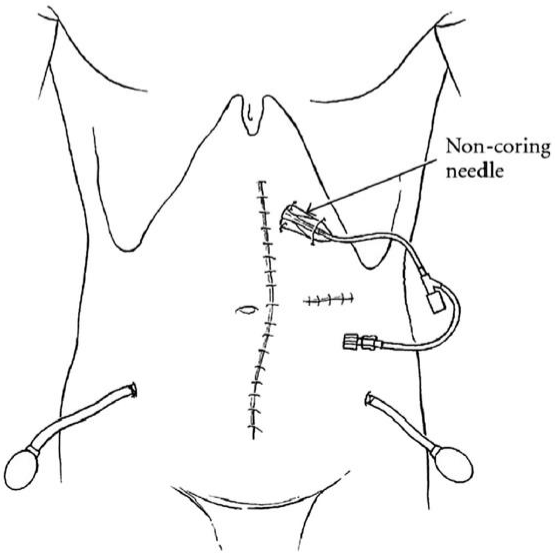

Figure 5b. Insertion of an intraperitoneal port at the time of pancreatic duodenectomy.

As seen in Figure 5b, a non-coring needle is used to maintain optimal position of the port for 10 days. Upon de-access, a peritoneal fluid specimen is obtained from the port for culture. The port is not flushed except prior to gemcitabine chemotherapy delivery. *(Modified from Ref. #24).*

2. The closed technique

It has been argued that the open technique has an exposure risk for the operating staff if breaches in clothing are present. Additionally, a fear of chemotherapy aerosolization has been described [60].

In the closed technique, both the inflow and outflow tubes are inserted into the abdomen and pelvis. The whole setup can be seen in Figure 6.

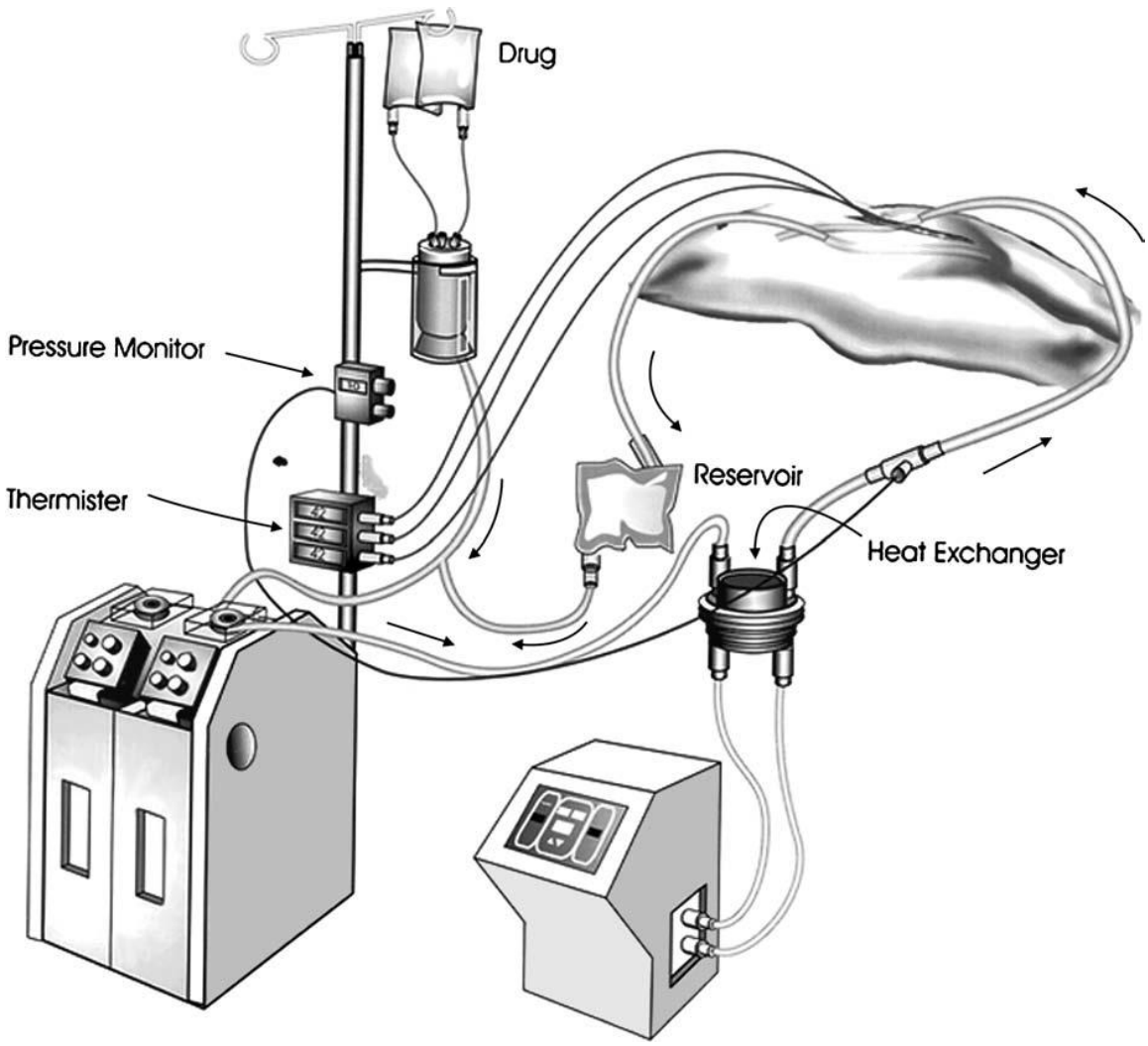

Figure. 6. Continuous hyperthermic peritoneal perfusion circuit. *(From Ref #62).*

Two to four large-bore catheters are inserted through the abdominal wall through the incision or percutaneously. The catheters are connected to a closed circuit consisting of a roller pump, a heat exchanger, and a reservoir. The temperature probes are placed beneath the peritoneal lining in order to monitor inflow and outflow temperatures, but if desired, they can also monitor internal locations. A watertight suture is used to temporarily seal the surgical incision. The chemotherapy fluid is heated and recirculated for approximately 90 minutes throughout the peritoneal cavity. In a usual flow configuration, the chemotherapy solution flows into the pelvis or the upper abdomen while the opposite location is used for the outflow [60]. (Figure 7).

The size of the peritoneal surface can vary related to the body surface area of the patient. The perfusion volume widely varies depending from many individual factors such as the patient size, the amount of ascites, and the extension of the resection. As a rule of thumb, a perfusion volume of approximately three liters is used for women while for men the volume is in the range of four liters. After confirming that no leaks are present and that the temperature is above 41^{o}C, the chemotherapy regimen is added to the circuit. During perfusion, the abdomen is gently shaken or massaged to achieve a uniform drug distribution [60].

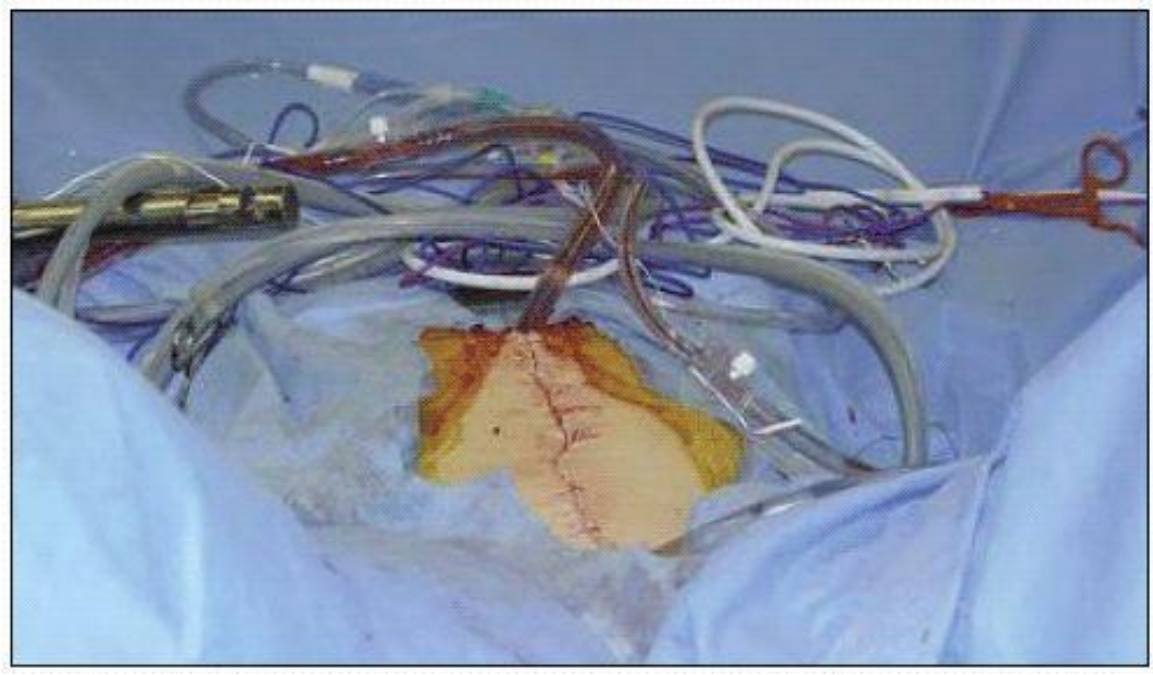

Figure 7. Closed HIPEC. Patient's abdomen prepared with inflow and outflow tubing. *(From Ref #60).*

Depending on the protocol, the perfusion time might range from 30 minutes [63] to two hours [59, 64], and varies between the different centers until some kind of standardization could be achieved. However, all protocols coincide that very high intraperitoneal chemotherapeutic concentrations are requested when compared to serum levels.

The whole procedure of HIPEC may last from 6 to 12 hours. The differences in HIPEC outcomes that have been reported are attributed to the differences in the regimens used [65]. This also suggests that HIPEC is an active component of the treatment. However, no clinical trials have addressed this issue so far.

Several chemotherapeutic agents have been used (mitomycin-C, cisplatin, etoposide etc.) [62]. Among them, the most potent restrictive agent against the progression of peritoneal metastases is intraperitoneal gemcitabine and that is why today it is almost exclusively used [66]. It has been shown that the median concentration area under the curve (AUC) of gemcitabine during intraperitoneal administration, was 209 times greater as compared to blood concentration, a finding showing the drug's increased intraperitoneal efficacy combined with a decreased systemic toxicity [67, 68].

Therefore, HIPEC gemcitabine following pancreatectomy and prior to intestinal reconstruction is indicated. Usual gemcitabine administration dose is 1000 mg/m^2 for 60 minutes at 42.5 – 43 ^{0}C [22, 69, 70, 71]. It is suggested that HIPEC gemcitabine can reduce peritoneal metastases in patients after pancreas cancer resection [24].

4.4. CRS + HIPEC

Today, the combination of complete CRS and HIPEC is established as the standard procedure in patients with malignant peritoneal disease. However, there are several drawbacks in this regimen as it is associated with an increased risk of surgical complications, due to the complexity of extensive surgery with multiple intra-abdominal organ resections and peritonectomies [72].

It has been shown that in cases with peritoneal metastases, the intraperitoneally administered chemotherapy may be effective to eliminate the microscopic residual cancer cells. Depending on the clinical scenario, this type of treatment can be used either for achieving a long-term remission or for palliation.

Appropriate patient selection for CRS and HIPEC is crucial. The ideal candidate must be in otherwise good condition to withstand such a long operation. If this is feasible, then age is not a limiting factor. Another factor is the completeness of cytoreduction, in other words to be able to remove all visible tumor deposits, as chemotherapy cannot penetrate larger tumor deposits. The following figure shows the level of completeness of cytoreduction (CC) up to which HIPEC is reasonably performed.

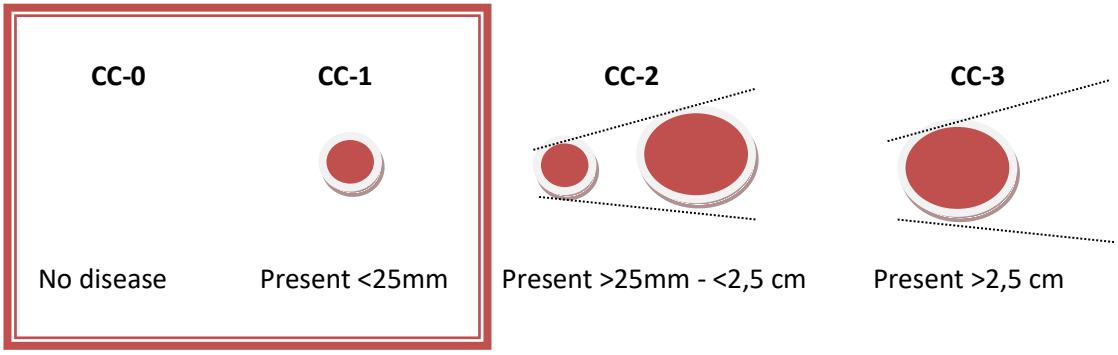

Figure 8. Up to CC-1 there is maximum benefit of HIPEC.

It has been shown that the outcomes for CRS + HIPEC are dependent from the primary site. Today CRS + HIPEC are considered as the preferred care for peritoneal cancer metastases stemming from colorectal cancer, cancer from the appendix [65, 73] pseudomyxoma peritonei [74], peritoneal mesothelioma [75], peritoneal sarcomatosis [76], or locally advanced ovarian cancer [77].

Regarding other primary gastrointestinal tract cancers, the recommendations are less clear due to the small numbers and variable case selection. Thus, the beneficial effect of HIPEC in peritoneal sarcomatosis has been debated [78], while the role of HIPEC in ovarian cancer does not appear to be clear [79].

However, it has been shown that the curative resection of pancreatic cancer combined with HIPEC has promising results as the local/regional failures are eliminated [70].

When it is not feasible to effectively manage the primary cancer, then the role of CRS + HIPEC is limited only to palliation purposes. In contrast, if the primary can be surgically excised and its peritoneal manifestation can be reasonably eradicated, the addition of HIPEC seems justified. Thus, in terms of palliation, a non-optimal debulking CRS with HIPEC can treat or prevent malignant ascites in 80 % to 90 % of cases [60].

4.5. Long-term normothermic intraperitoneal chemotherapy (NIPEC-LT)

NIPEC-LT gemcitabine in conjunction with HIPEC has been used to treat liver and lymph node micrometastases. However, it seems that a single gemcitabine treatment is not enough to control them and therefore repeated intraperitoneal instillations are needed as shown below in Table 7.

Table 7. Regimen for long-term normothermic intraperitoneal gemcitabine.

Long-term normothermic intraperitoneal gemcitabine:
• Intraperitoneally through the intraperitoneal port. Instill the fluid by programmed pump at 999 ml/h or as tolerated by the patient and do not drain. • Dose of gemcitabine is 1000 mg/m^2 in 1 L of 1.5 % dextrose peritoneal dialysis solution. • Schedule is: Day 1, 8 and 15 of every month for a total of 6 cycles.

Modified from Ref #24.

Up to now, very few cases of resected pancreatic carcinomas have been treated with HIPEC and NIPEC-LT gemcitabine. However, it has been reported that the survival at three years is 50 % and the patterns of surgical treatment failure are markedly changed [24]. Therefore, this approach deserves more studies.

OUR CONTRIBUTION (SPECIFIC SESSION)

5. Aim

To conduct a systematic review on whether the combination of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (CRS/HIPEC) has a place in the treatment of pancreatic adenocarcinoma.

6. Methods

6.1. Search Strategy

This systematic review was conducted by searching medical literature in MEDLINE and SCOPUS, guided by the PRISMA protocol [80, 81]. The last search was conducted in January 2018. All the retrieved article titles and abstracts were screened for relevant manuscripts. A full text review of the selected relevant articles was made to detect the studies included in this systematic review. Relevant full text review manuscripts or systematic review manuscripts were used to retrieve relevant articles from their reference list, if any.

Medical Subject Heading (MeSH) terms and text words were used based on the following search strategy:

Group A terms: “crs” OR “cytoreduction” OR “cytoreductive surgery” OR “debulking” OR “hipec” OR “hyperthermic intraperitoneal chemotherapy”.

Group B terms: “pancreas” OR “pancreatic”.

Group A and group B terms were combined, and no limits were applied.

6.2. Inclusion – exclusion criteria

Of the articles retrieved through the above described search strategy only those that met the following criteria were included to this systematic review:

1. Studies on CRS/HIPEC treatment for pancreatic cancer with or without peritoneal carcinomatosis of pancreatic cancer origin were included.
2. Case reports were included, to include all reported relevant cases.
3. Case series and/or original papers from the same research team were included and care was taken for not to include duplicate cases.
4. Review articles and/or meta-analyses and/or book chapters were excluded.

7. Results

The search strategy after duplicates were removed yielded 1100 articles. Of these articles 1060 were excluded according to the predefined criteria through title and abstract screening. There were 40 articles selected for full text review.

Thirty-one of them were also excluded as not relevant (n = 2), reviews/editorials/book chapters (n = 7), animal studies (n = 1), no CRS/HIPEC (n = 8) or no pancreatic cancer (n = 13). The remaining nine articles were included to the study. No additional relevant articles were identified from the reference list of the reviews.

The flow diagram of the selection process is shown in Figure 9.

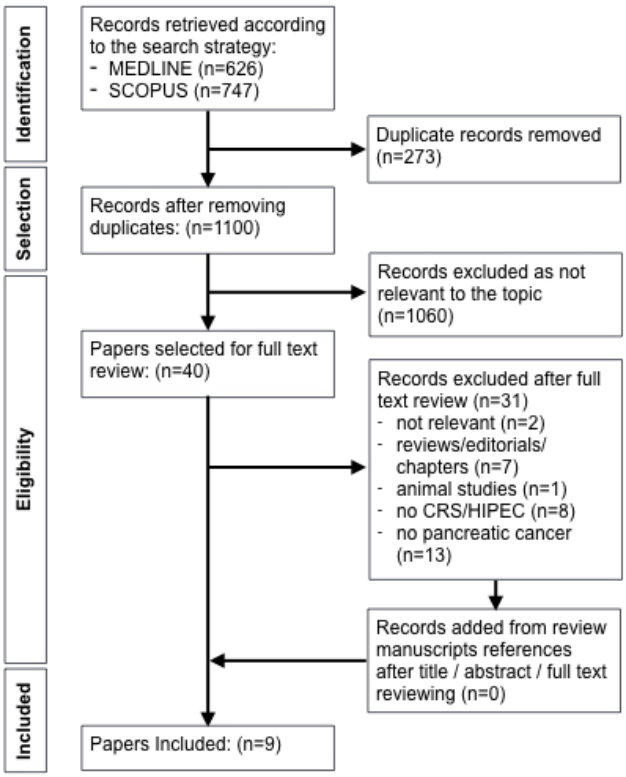

Figure 9: The flow diagram of our systematic review.

The characteristics of the included studies are presented in Table 8.

Table 8. The final nine papers included to this systematic review.

Article	Authors	Article type	# of pancreatic cancer cases	Sex	Peritoneal Carcinomatosis	Tumor original location	Histology	PCI	CC	OS	Morbidity	Mortality
1	Arjona-Sanchez et al, 2014	CR	1	F	Yes - metachronous	Tail	Mucinous adenocarcinoma	20	CC-0	70 months	0 %	0 %
2	Berger et al, 2016	RC	2	N/A	Yes – no other data available	N/A	adenocarcinoma	N/A	N/A	N/A	N/A	N/A
3	Farma et al, 2005	RC	7	N/A	Yes – 3 synchronous, 4 metachronous	Head 2 Tail 1 N/A 4	adenocarcinoma	N/A	CC-0 n=6 CC-2 n=1	2-62 months	57 %	0 %
4	Fujimura et al, 1999	RC	1	M	Yes - metachronous	N/A	adenocarcinoma	N/A	N/A	18 months	0 %	0 %
5	Goere et al, 2017	RC	*32 (14 not in other studies)	N/A	Yes – no other data available	N/A	adenocarcinoma	N/A	N/A	N/A	N/A	N/A
6	Levine et al, 2014	RC	6	N/A	Yes – no other data available	N/A	adenocarcinoma of Cystic and IPMT origin	N/A	N/A	N/A	N/A	N/A
7	Schwarz et al, 2016	RC	3	N/A	Yes – no other data available	Tail	adenocarcinoma	N/A	N/A	N/A	N/A	N/A
8	Tentes et al, 2012	RC	21	9 M, 12 F	Yes: n = 1 synchronous No: n = 20	Head 17 Body 1 Tail 3	adenocarcinoma	N/A	CC-1	5-year: 23 %	33.3 %	9.5 %
9	Tentes et al, 2016	RC	33 (13 not in other studies)	14 M, 19 F	No	Head 26 Body 2 Tail 4 Mixed 1	adenocarcinoma	Not applic-able	Not applic-able	5-year: 24 %.	24.2 %	6.1 %

Legends

M: Male, **F:** Female, **CR:** Case Report, **RC:** Retrospective Cohort, **OS:** Overall Survival, **PCI:** Peritoneal Cancer Index,

CC: Completeness of Cytoreduction, **IPMT:** Intraductal Papillary Mucinous Tumor, **N/A:** Not Available.

* Data from this study were considered according to the text. There is a mismatch in text and table numbers.

The final nine papers included to the systematic review were two retrospective cohorts of pancreatic cancer cases treated with CRS/HIPEC [70, 22], six retrospective cohorts of CRS/HIPEC cases that included some pancreatic cancer cases [82, 62, 83, 84, 65, 72] and one case report [85]. These nine studies included 68 cases of pancreatic cancer treated with CRS/HIPEC, after duplicate cases were removed. Thirty-three cases from one study [22] received CRS/HIPEC as an adjuvant for resectable pancreatic cancer with no peritoneal disease (TNM I: 4, TMN II: 9, TNM III: 20), while the rest 35 cases had peritoneal carcinomatosis of pancreatic cancer origin and treated with CRS/HIPEC. These cases with peritoneal carcinomatosis of pancreatic origin included six cases with metachronous peritoneal metastases. Four cases with synchronous peritoneal metastases, and 25 cases with no data available. None of the studies included any kind of comparison group. The data regarding gender and age were not available in more than the half of the studies included. The location of the original pancreatic tumor was available in 41 cases (28 head, 2 body, 10 tail, 1 mixed). Regarding the histology type of the tumor present in the studies included, adenocarcinoma of the pancreas was noted in seven studies [22, 62, 70, 72, 82, 83, 84]. In the study of Arjona-Sanchez et al, 2014, it was mucinous adenocarcinoma [85], and for the study of Levine et al, 2014, it was peritoneal carcinomatosis derived from adenocarcinoma of cystic neoplasms and intraductal papillary mucinous tumors origin [65].

The technique used was not available for the studies of Arjona-Sanchez et al, 2014, [85], Goere et al, 2017 [84] and Schwarz et al, 2016 [72]. The open and the closed techniques was used for in three studies each. The closed technique was used in the studies of Farma et al, 2005, [62] Levine at el, 2014, [65] and Berger et al, 2016 [82]. In the studies of Tentes et al, 2012, [70], Tentes et al, 2016, [22] and Fujimura et al, 1999, [83], the open technique was used.

Regarding the HIPEC chemotherapeutic agent used, two studies [85, 65] reported the use of Mitomycin C (MMC), one study [83] a combination of MMC with cisplatin and etoposide, one study [56] cisplatin alone, two studies gemcitabine [70, 22] and three studies [82, 84, 72] provided limited data regarding pancreatic cancer cases.

More data regarding the, dosage, dialysate, temperature and HIPEC duration are presented in the Appendix (Table A10). In more detail, the type of drug used was not available in three of the nine studies included in this review [72, 82, 84]. In two studies Mitomycin C was used [65, 85]. Two studies used Gemcitabine as the drug of choice [22, 70] and one study used Cisplatin [62]. In the study of Fujimura et al, 1999, a combination of Cisplatin, Mitomycin C and Etoposide was used [83].

In terms of drug dosage, the dosages were different in all the studies. The three studies that did not state the type of drug administered, the dosage was also not mentioned [72, 82, 84]. The two studies which used only Gemcitabine as drug of choice, the dosage used in each study was 1000 mg/m^2 [22, 70]. In the study of Arjona-Sanchez et al, 2014, 30 mg of Mitomycin C was administered [85]. The other study that used Mitomycin C was that of Levine et al, 2014, which used 40 mg [65]. Farma et al, 2005, used 425 – 676 mg/m^2 Cisplatin [62]. In the study of

Fujimura et al, 1999, where a combination of Cisplatin, Mitomycin C and Etoposide was used 300 mg, 60 mg and 100 mg of drug dosage was administered respectively [83].

The type and kind of solution used was available only for three of the studies. These were the studies of Arjona-Sanchez et al, 2014 in which 15% solution was used [85], the study of Fujimura et al, 1999, were Saline was used [83], and that of Levine at el, 2014, were Ringer's Lactate or Plasma was used [65].

As far as the volume of solution used, it was not available in four studies [72, 82, 83, 84]. In the remainder of the studies it ranged from 2000-7000 ml. Arjona-Sanchez et al, 2014, used a volume of 4000 ml [85], Farma et al, 2005, used 3000 – 7000 ml [62], Levine at el, 2014, used 3000 ml [65], in the study of Tentes et al, 2012, 2000 – 3000 ml was used [70], and in Tentes et al, 2016, study 3000 ml was used [22].

Data on the temperature and duration of infusion was once more not available for three of the nine studies included [72, 82, 84]. For the remaining six studies, the temperature ranged from 40 ^{0}C to 43 ^{0}C and the duration from 60 to 120 minutes. In the study of Arjona-Sanchez et al, 2014, the temperature was 42 ^{0}C and the duration was 60 minutes [85]. In the study of Farma et al, 2005, the temperature used was 41,4 ^{0}C for 90 minutes [62], and in the study of Fujimura et al, 1999, the temperature ranged from 42 – 42,5 ^{0}C for 60 minutes [83]. Levine at el, 2014, used a temperature of 40 ^{0}C and 120 minutes in duration [65]. The study of Tentes et al, 2012, the duration was 60 minutes at a temperature of 42 – 43 ^{0}C [70], and in the study of Tentes et al, 2016, the duration was once again 60 minutes, but the temperature ranged from 42,5 – 43 ^{0}C [22].

Table 9. Data regarding the open/closed technique, dosage, dialysate, temperature and HIPEC duration of the nine studies. (Study numbers refer to those of Table 8)**.**

Study #	Technique	Drug	Drug dose	Solution	Solution Volume	Temp	Duration
1	N/A	MMC	30 mg	15 %	4000 ml	42 ^{0}C	60 min
2	C	N/A	N/A	N/A	N/A	N/A	N/A
3	C	Cisplatin	425-676 mg/m^2	N/A	3000-7000 ml	41,4 ^{0}C	90 min
4	O	Cisplatin + MMC + Etoposide	300 mg 60 mg 100 mg	Saline	N/A	42-42,5 ^{0}C	60 min
5	N/A	N/A	N/A	N/A	N/A	N/A	N/A
6	C	MMC	40 mg	RL or Plasma	3000 ml	40 ^{0}C	120 min
7	N/A	N/A	N/A	N/A	N/A	N/A	N/A
8	O	Gemcitabine	1000 mg/m^2	N/A	2000-3000 ml	42-43 ^{0}C	60 min
9	O	Gemcitabine	1000 mg/m^2	N/A	3000 ml	42,5-43 ^{0}C	60 min

Legends:

N/A: Not Available, **O:** Open technique, **C:** Closed technique, **RL:** Ringer's Lactate,

MMC: Mitomycin C.

The overall survival (OS) of pancreatic cancer peritoneal carcinomatosis treated with CRS/HIPEC is reported in nine out of 35 cases, as of 2 to 70 months. The group of 33 cases of pancreatic cancer and no peritoneal carcinomatosis treated with CRS/HIPEC had an overall mean and median survival of 33 and 13 months, respectively (5-year survival 24 %), with a median follow-up of 11 months. The recurrence rate was 60.6 % (20 patients) with three patients having local (regional) recurrence (9.1 %) and the rest of them liver metastases.

Morbidity and mortality available data is presented in Table 9.

8. Discussion

The main obstacle of the cancer of pancreas treatment is its low resectability rate which at best arrives up to 10 – 15 % of the diagnosed tumors [12, 13, 14, 15]2. Additionally, some other cases have locally resectable tumors but already manifest distant metastases at the time of initial diagnosis [22].

Therefore, different treatment modalities have been used for the treatment of pancreatic adenocarcinoma. Among them, chemotherapy is the standard of care for non-resectable disease, as previously presented. However, the advancement in operative, anesthetic, and chemo-agents fields have not provided patients with a better prognosis, over the past years [16, 17, 18, 24, 25].

In this respect, HIPEC has been lately used for pancreatic adenocarcinoma treatment, based on the rationale that very high drug IP concentrations can be achieved limiting systemic toxicity [60].

In this study we aimed to systematically review the available literature regarding this approach in the management of pancreatic adenocarcinoma.

As it can be seen in the results section, only nine studies met the criteria. This very limited bibliography indicates that there is much more research needed towards the use of HIPEC in pancreatic adenocarcinoma.

Duplicate cases

Since there is scarce bibliography about cytoreductive surgery and HIPEC in the treatment of pancreatic adenocarcinoma, from the nine papers included in this systematic review, a duplicate number of pancreatic cancer cases were found.

The papers published from authors of the same team or reanalyzed data from authors with previous publications on this subject were carefully compared to identify duplicate cases, when possible. The retrospective cohort study of Goere et al, 2017, contained 32 cases of pancreatic cancer from which 14 cases were not included in other studies [84]. In this study the data were provided from several centers that perform CRS and HIPEC. The cases that considered as duplicates were those provided from centers that had already published on this subject before the publication of Goere et al paper.

Tentes et al, 2016, [22] is a retrospective study that presents a larger cohort of patients extending the results of a previous published study, i.e. Tentes et al. 2012 [70]. It contains a

total of 33 pancreatic cancer cases, with 13 cases not included in the 2012 paper. Only one case in Tentes et al, 2012, [70] was not included in the later study carried out in 2016 by Tentes et al [22] due to different inclusion-exclusion criteria among the two studies.

Thus, our in-depth analysis of the nine studies revealed that after duplicate cases removed, only 68 patients with pancreatic cancer were treated with CRS/HIPEC.

Data availability: Subgroups of pancreas adenocarcinoma patients within other cases.

From the nine included studies, only three were focused on CRS and HIPEC in terms of pancreatic cancer patients. These studies were those of Arjona-Sanchez et al, 2014 [85], Tentes et al, 2012 [70] and Tentes et al, 2016 [22]. The remaining six studies [62, 65, 72, 82, 83, 84], included some cases of pancreatic cancer patients but without specific focus on the pancreas itself. This therefore shows that the availability of the data was scarce and even in a few of these studies, pancreatic cancer patients were grouped as other cases [82, 83].

The data regarding gender and age were not available in more than the half of the studies included. The original tumor location was only available in five studies [22, 62, 70, 72, 85]. Peritoneal Cancer Index (PCI) was only available for one study [85], and in the remainder of the studies, the mean or the median Peritoneal Cancer Index was used whenever available.

The tumor original location was not available in four studies [65, 82, 83, 84]. In the remaining five studies, the tumor location of the pancreatic cases was available in terms of the anatomy of the pancreas, i.e. head, body, tail and mixed.

Difficulties were also seen in classifying Completeness of Cytoreduction (CC), where specific data was available in only three out of the nine studies [62, 70, 85]. For the remaining studies the Completeness of Cytoreduction was either not mentioned, not applicable, not available or once again as for the Peritoneal Cancer Index, the mean or median was used.

The HIPEC technique (open or closed) used was not available for the studies of Arjona-Sanchez et al, 2014, [85], Goere et al, 2017 [84] and Schwarz et al, 2016 [72]. The type of drug used was not available in three of the nine studies included in this review [72, 82, 84].

Data heterogeneity.

As far as data heterogeneity is concerned in the studies included to this review, a few points can be made:

The nine studies included vary greatly in terms of design. Due to the extremely limited literature on the subject, all kinds of manuscripts were included. Thus, case reports, cases of pancreatic adenocarcinoma studied among other rare indications for CRS/HIPEC, and studies focused on

CRS/HIPEC and pancreatic adenocarcinoma were analysed. Only three studies [22, 70, 85], focused primarily on CRS/HIPEC in pancreatic cancer patients while the remaining studies included them together with other cancer cases treated with CRS/HIPEC.

Data heterogeneity was also present in terms of peritoneal carcinomatosis amongst the studies included. In the study of Tentes et al, 2016, there was no peritoneal carcinomatosis in all cases of pancreatic cancer [22] whereas in the previous study of Tentes et al, 2012, one case was synchronous and for the remaining ones there was no peritoneal carcinomatosis [70]. In two studies, the peritoneal carcinomatosis was metachronous [83, 85]. In the study of Farma et al, 2005, there was peritoneal carcinomatosis with nearly half the patients being synchronous and the other half metachronous [62]. In the remaining four studies included in this review, although there was peritoneal carcinomatosis, no further data was available in terms of synchronous or metachronous [65, 72, 82, 84].

Also, the drug regiments, the solutions, and the hyperthermia temperature used for the HIPEC treatment varied greatly.

Furthermore, 1/3 of the studies do not comment on the two different variations of HIPEC application (open and closed technique) [24, 60, 61], while half of the remaining studies used the open and half the closed technique.

CRS/HIPEC as treatment of peritoneal carcinomatosis from pancreatic adenocarcinoma.

CRS and HIPEC is considered the surgical treatment that can achieve considerable survival benefit in several histologies of peritoneal carcinomatosis, such as peritoneal mesothelioma [86], pseudomyxoma peritonei [87], peritoneal carcinomatosis of colorectal origin [88] or appendiceal adenocarcinoma [89], and ovarian cancer [90]. In six studies of this systematic review, the 35 patients reported suffered peritoneal carcinomatosis from pancreatic adenocarcinoma.

In the case of peritoneal carcinomatosis of exocrine pancreatic origin, the data that are available according to this systematic review are very limited and far from any suggestions or comparisons to be made: Four patients had OS less than a year after CRS & HIPEC. Another three patients had up to two years of OS, while two patients reached more than 5-year OS.

Questions raised on pancreatic cancer with peritoneal carcinomatosis patients' selection suitable for CRS & HIPEC in terms of histology, primary tumor location, PCI score, previous operations and synchronous or metachronous peritoneal disease or CC-score cannot be answered. Also, survival benefit, if any, cannot be supported based on current data.

CRS/HIPEC as prevention of peritoneal carcinomatosis from pancreatic adenocarcinoma.

In two studies from the same group [22, 70], the 33 patients reported presented pancreatic adenocarcinoma without peritoneal carcinomatosis. These patients were treated surgically undergoing resection of the primary tumor and HIPEC. The 5-year OS was 24 % and the morbidity and mortality rate was 24.2 and 6.1 %, respectively. These results show an acceptable morbidity and mortality rate compared with pancreatectomies [91].

Also, the overall survival rate reported is among the highest in the pancreatic cancer literature, considering that resectable disease has a 7 – 25 % 5-year OS rates, depending on the stage [6 - 11].

This retrospective cohort of 33 patients, even with the limitations that come with the study design, points towards the need of further investigation of the application of upfront HIPEC in resectable pancreatic cancer.

Future directions.

CRS & HIPEC has made a course of more than 35 years as peritoneal carcinomatosis treatment. Tumors that used to be considered unresectable may receive CRS & HIPEC with clear survival benefit, depending on the histology of the primary disease among other factors. The palliative approach to peritoneal carcinomatosis has changed since the implementation of CRS and HIPEC. However, there are some histologies that do not seem to respond to the concept of CRS and HIPEC. One of the less studied histologies is this of the pancreatic adenocarcinoma. The data presented in this systematic review only point to the fact that further investigation is needed before any safe conclusions can be made, especially for the concept of treating peritoneal carcinomatosis of pancreatic adenocarcinoma origin.

Indeed, though, it is interesting that there is a series of patients with prophylactic use of HIPEC after R0 resection of pancreatic adenocarcinoma without peritoneal disease. This approach is innovative in pancreatic cancer treatment. The survival results are among the higher in the pancreatic cancer literature. However, these results should be perceived with caution in terms of stage relative survival, reproducibility, morbidity and mortality, and cost effectiveness.

It has to be noted that more studies are needed. Well-designed RCTs should focus on answering questions regarding the burden of disease that is amenable to CRS & HIPEC treatment, which drug is the best, what is the optimal dosage and drug solution, which is the optimal temperature for HIPEC. Although theoretically, the effect of increasing hyperthermia is an especially easy to study clinically variable, such as a randomized trial of chemotherapy infusion at 37 ^{0}C vs 42 ^{0}C, has not been performed so far. Thus, the advantage of increasing the HIPEC temperature remains unproven [60].

The additional cost of HIPEC to “standard” surgery is low: It is probably less than that of a month of conventional systemic therapy and certainly much more less than that of therapy with biologic agents. Expenses include the cost of operating room time for the perfusion set-up and perfusion time, the cost of supplies, and cost of the drugs. However, it must be taken into account that the abovementioned costs are not repeatable, since CRS and HIPEC is typically a one-time treatment. [60].

Nowadays, it is apparent that a bigger number of oncology surgeons are trained in CRS and HIPEC and additionally more hospitals are creating specialized teams to offer this approach. Therefore, it seems that CRS and HIPEC will flourish in the years to come.

Additionally, since the combination of HIPEC and NIPEC-LT has been proven beneficial to other types of cancers with peritoneal involvement, it is expected that HIPEC and NIPEC-LT gemcitabine for pancreatic cancer is worth of further research [24]. Furthermore, new HIPEC drug combinations, such as incorporating systemic abraxane into the NIPEC-LT gemcitabine regimen to patients who acquire reasonable tolerance to long-term gemcitabine, is worth for further studies [24].

According to clinical trials registry ClinicalTrials.gov, there are 2 clinical trials on pancreatic cancer and HIPEC that have been registered. The first one (ClinicalTrials.gov Identifier: NCT02850874) designed to study HIPEC as neoadjuvant treatment in pancreatic adenocarcinoma was withdrawn due to no recruitment. The other one (ClinicalTrials.gov Identifier: NCT03251365) designed to study CRS/HIPEC for locally/regionally resectable pancreatic adenocarcinoma is still recruiting.

9. Conclusions

Pancreatic adenocarcinoma prognosis is still unfavorable. The recent advancements in chemotherapy agents, anesthesiology, and surgery have not presented themselves as game changers. As the resectability of the tumor seems to be the most important factor of prognosis, the application of CRS & HIPEC seems a reasonable approach; however, the extremely limited data prevent to draw any safe conclusions.

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APPENDIX

Table A1: Clinical presentation initial workup.

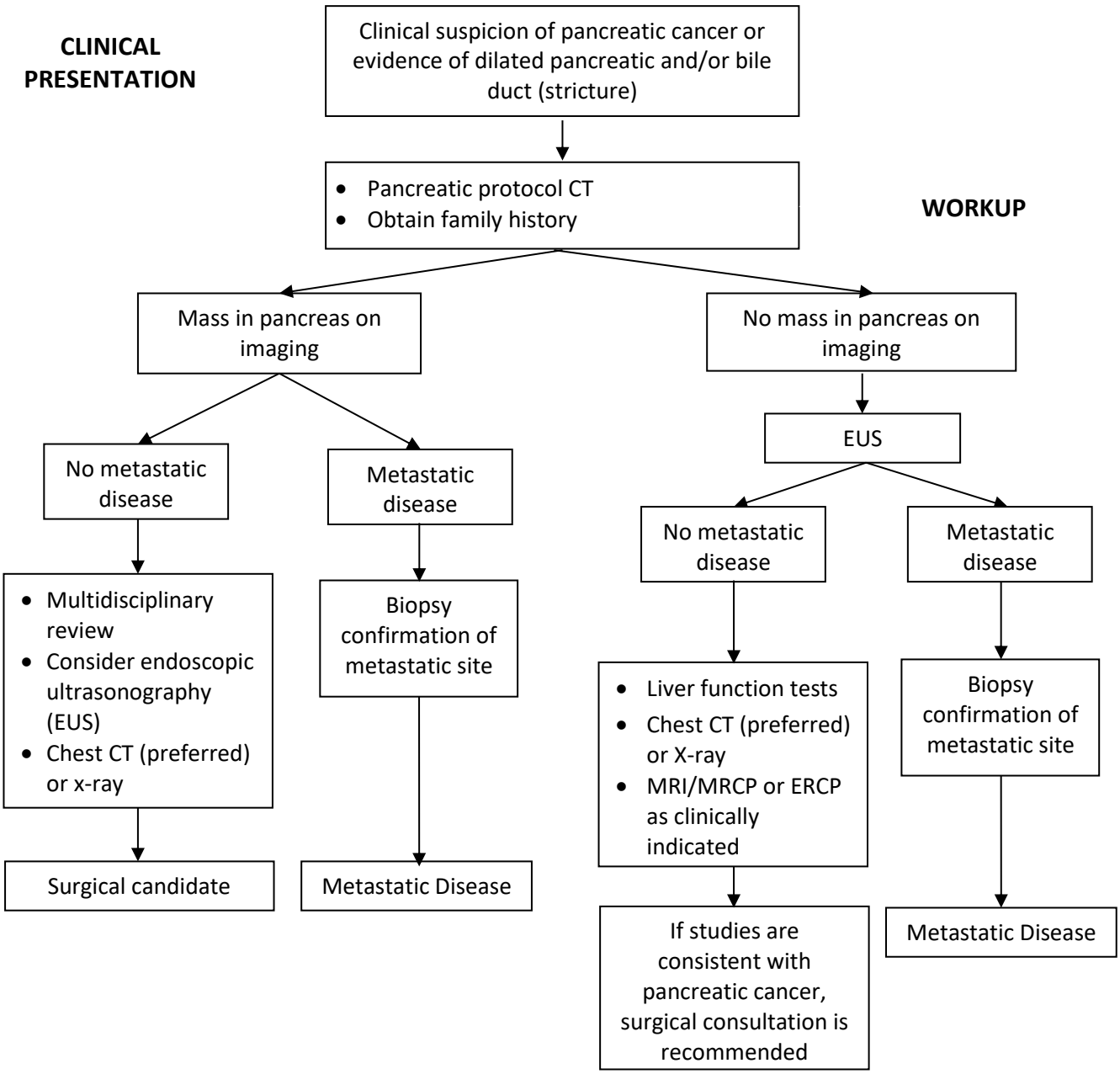

Table A2: Surgical candidate workup.

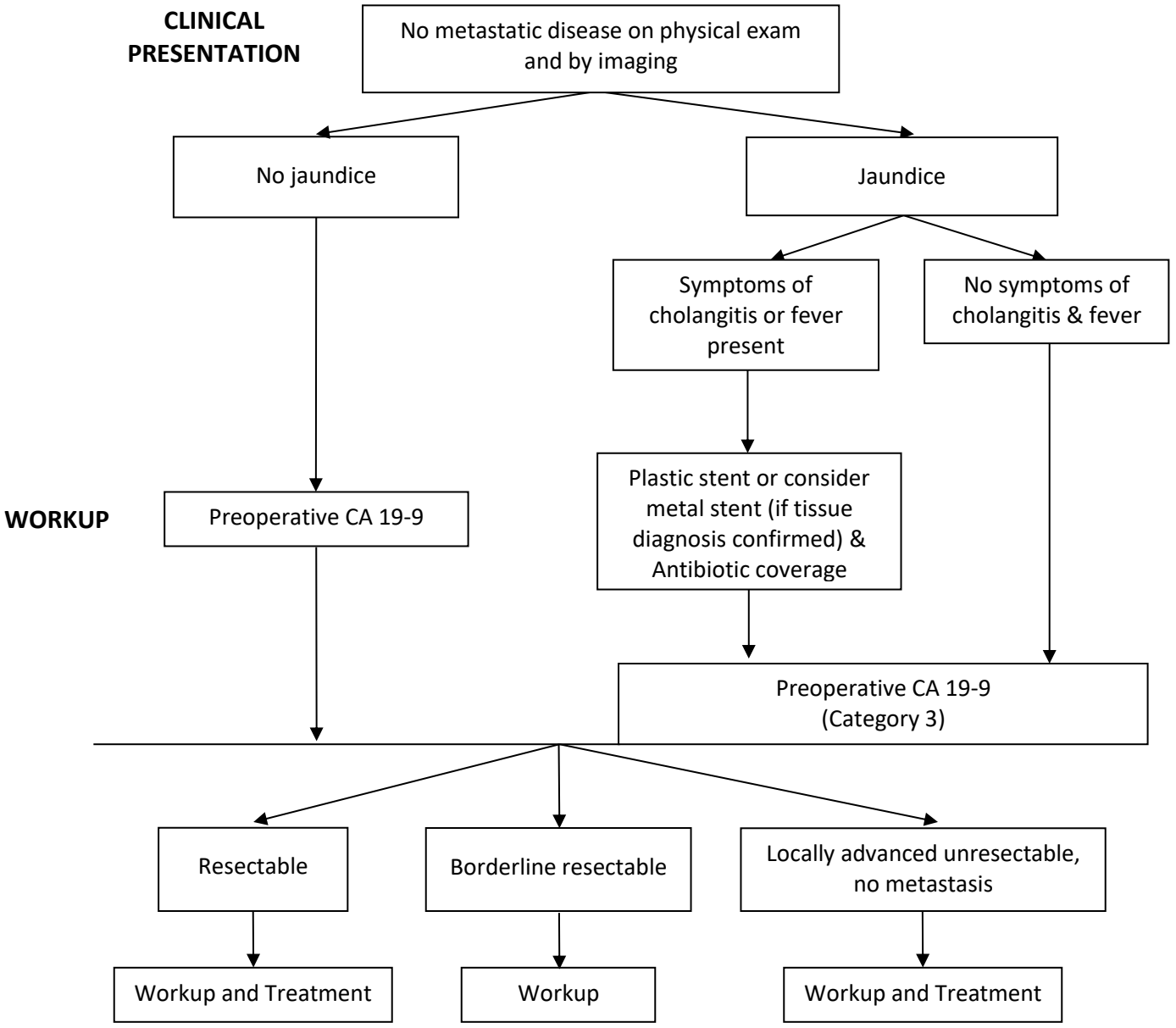

Table A3: Resectable candidate workup.

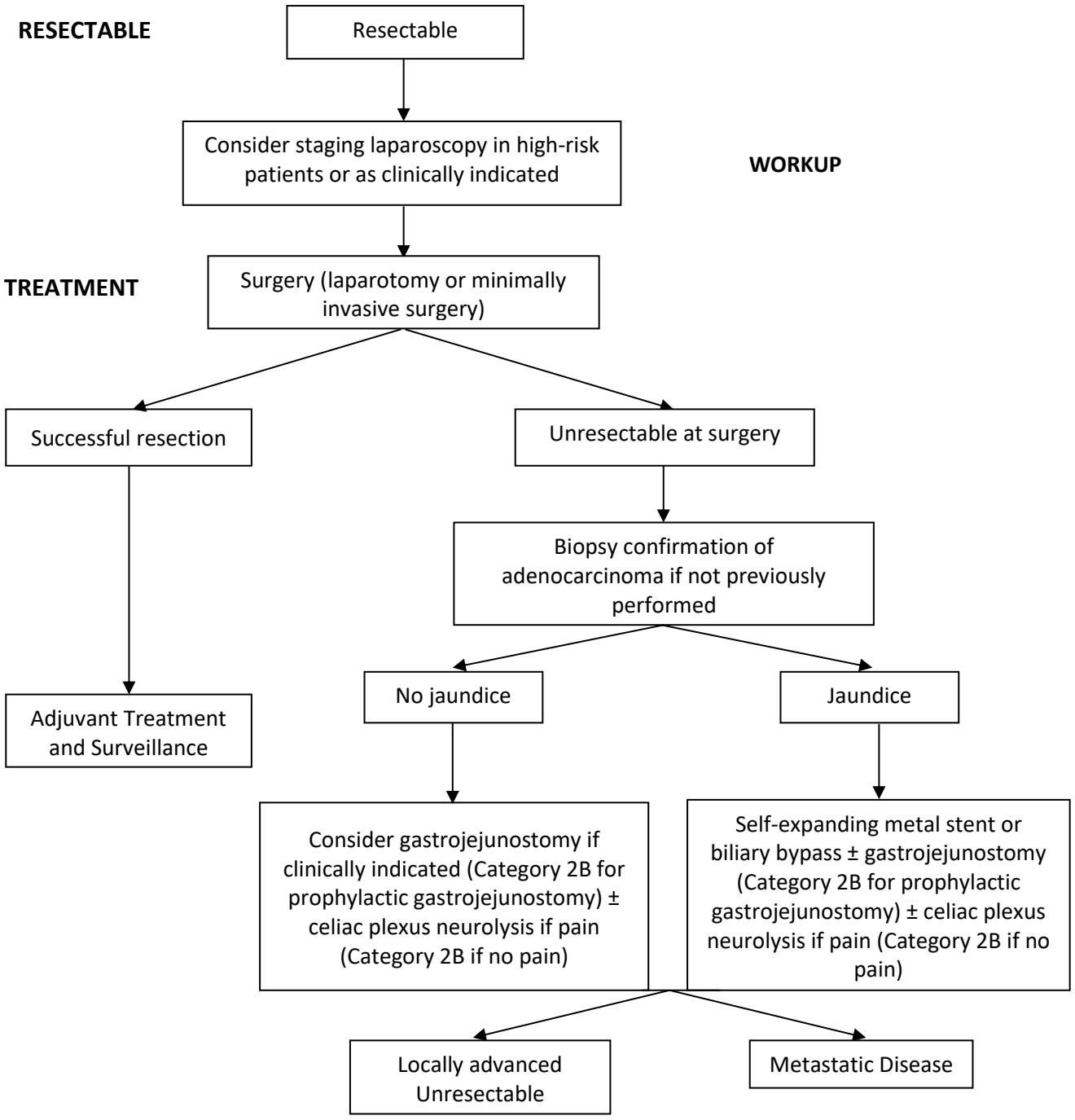

Table A4: Borderline resectable no metastasis workup.

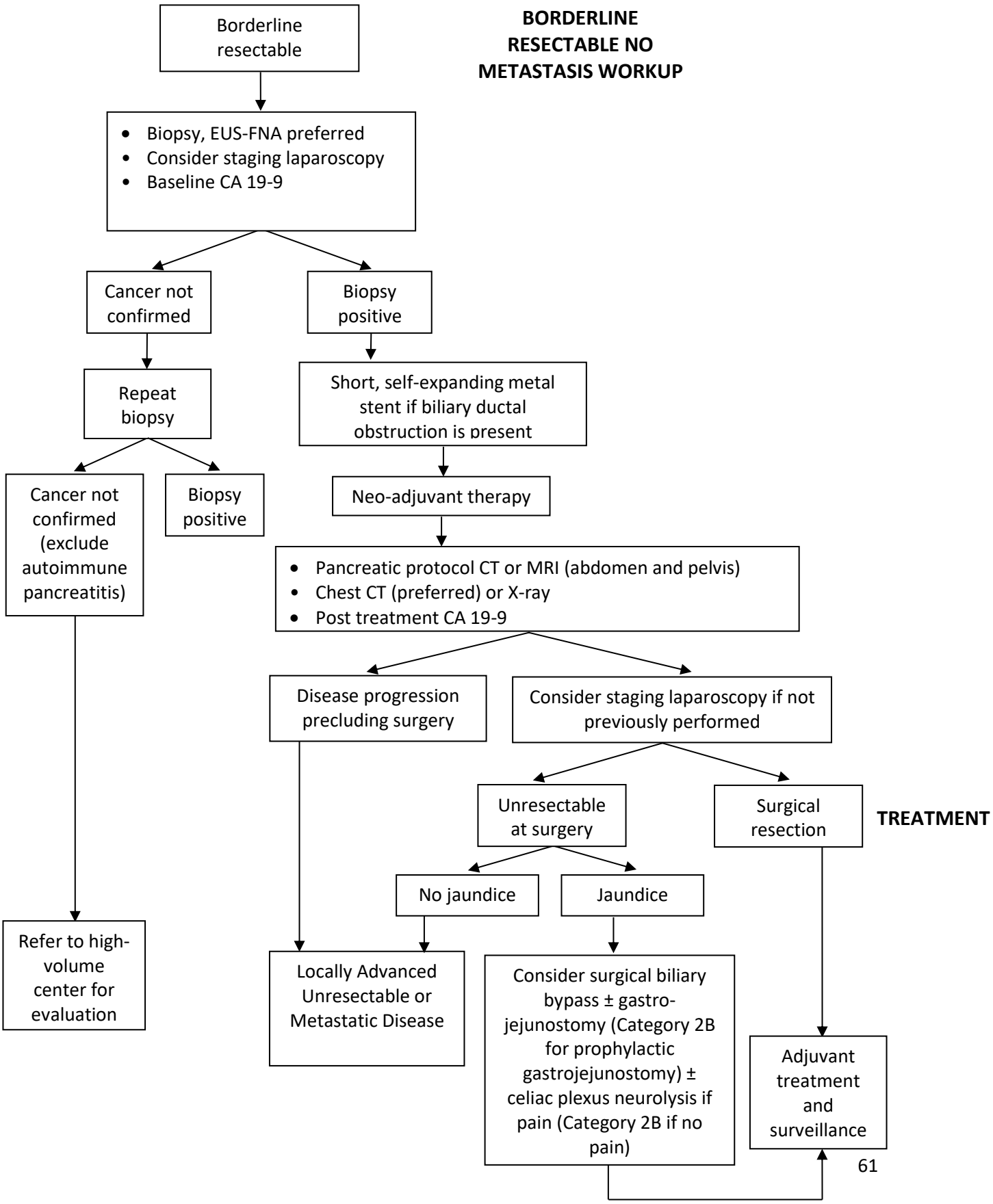

Table A5: Postoperative adjuvant treatment and surveillance.

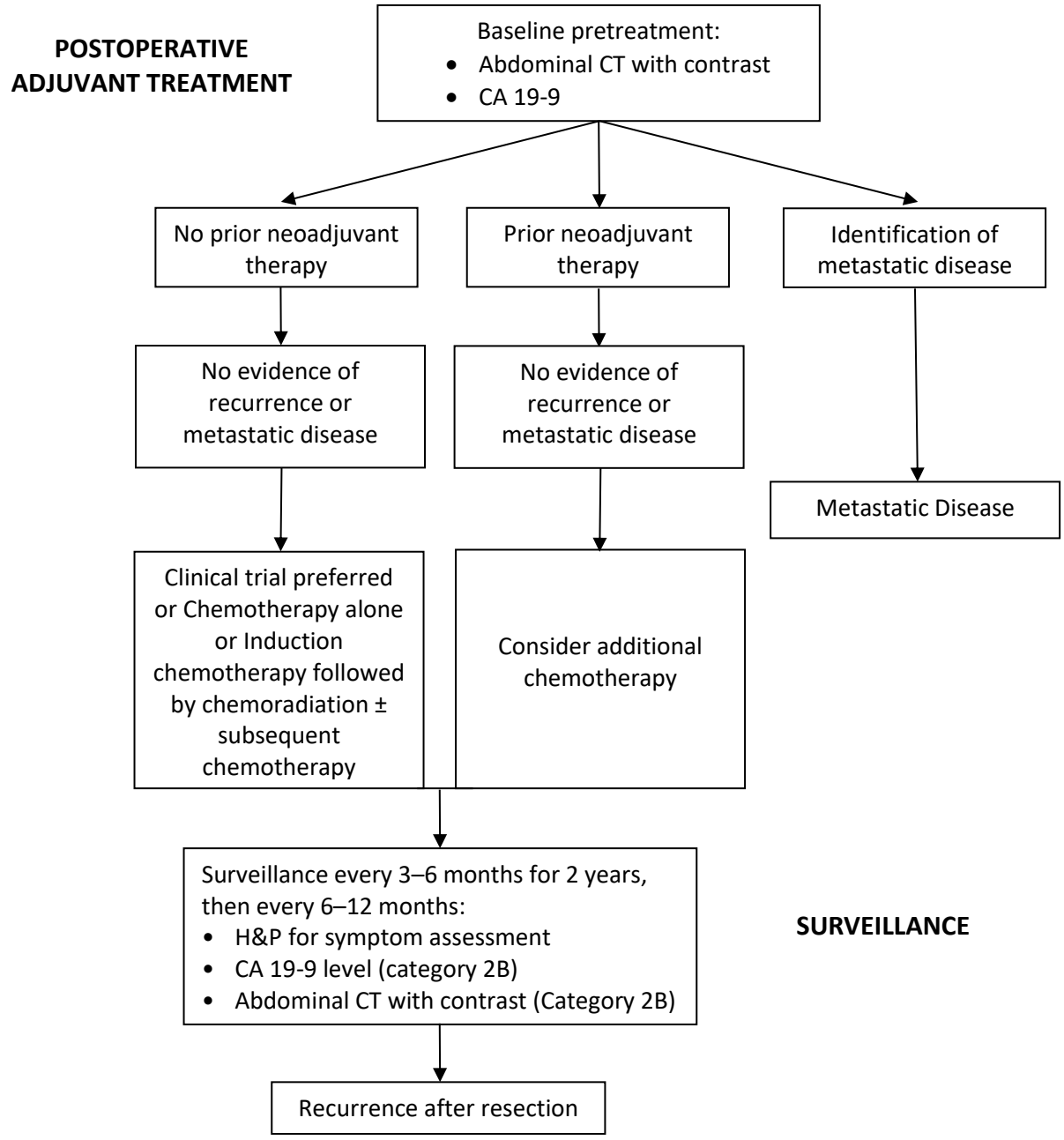

Table A6: Locally advanced unresectable workup.

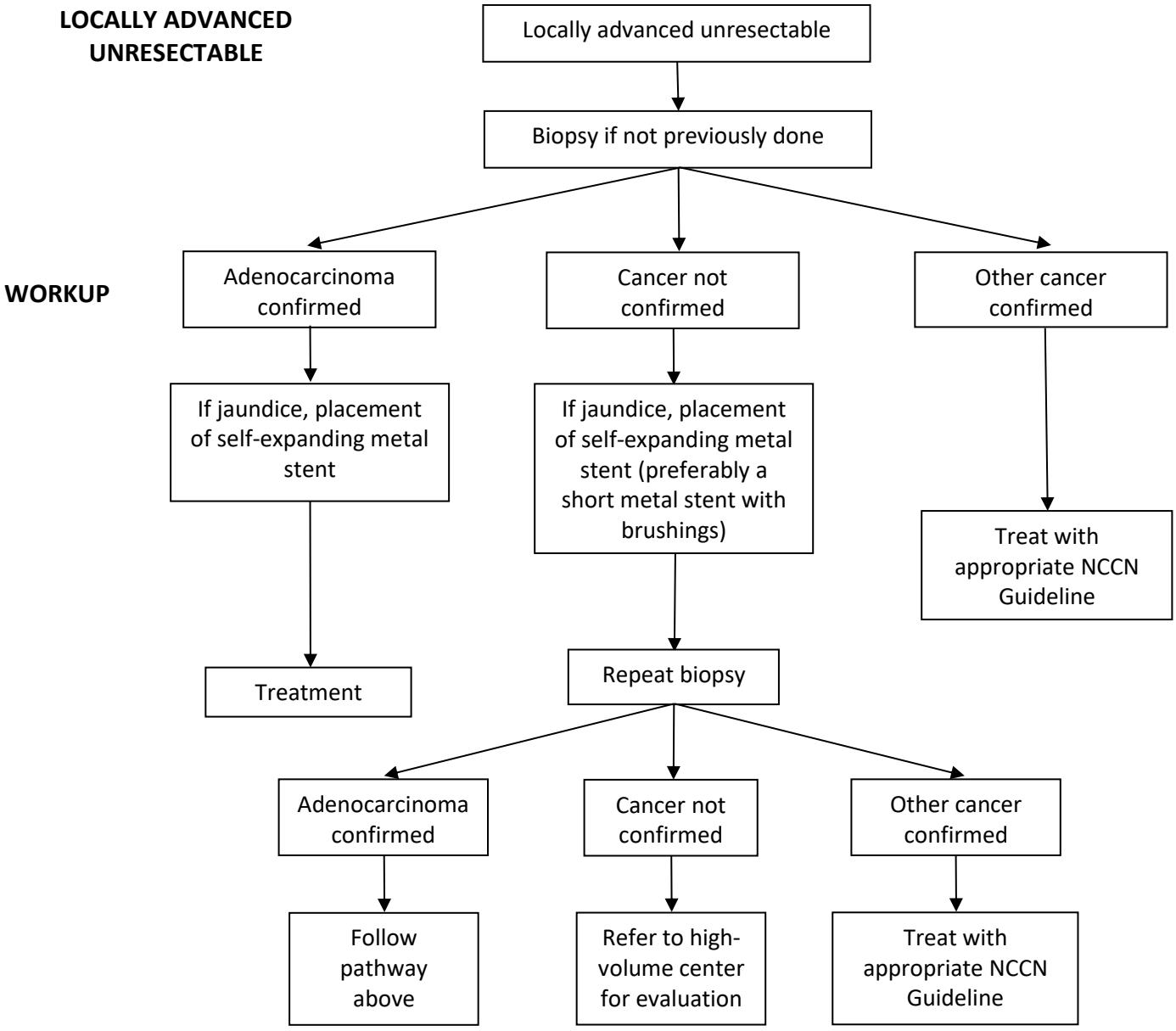

Table A7: Locally advanced unresectable lines of treatment.

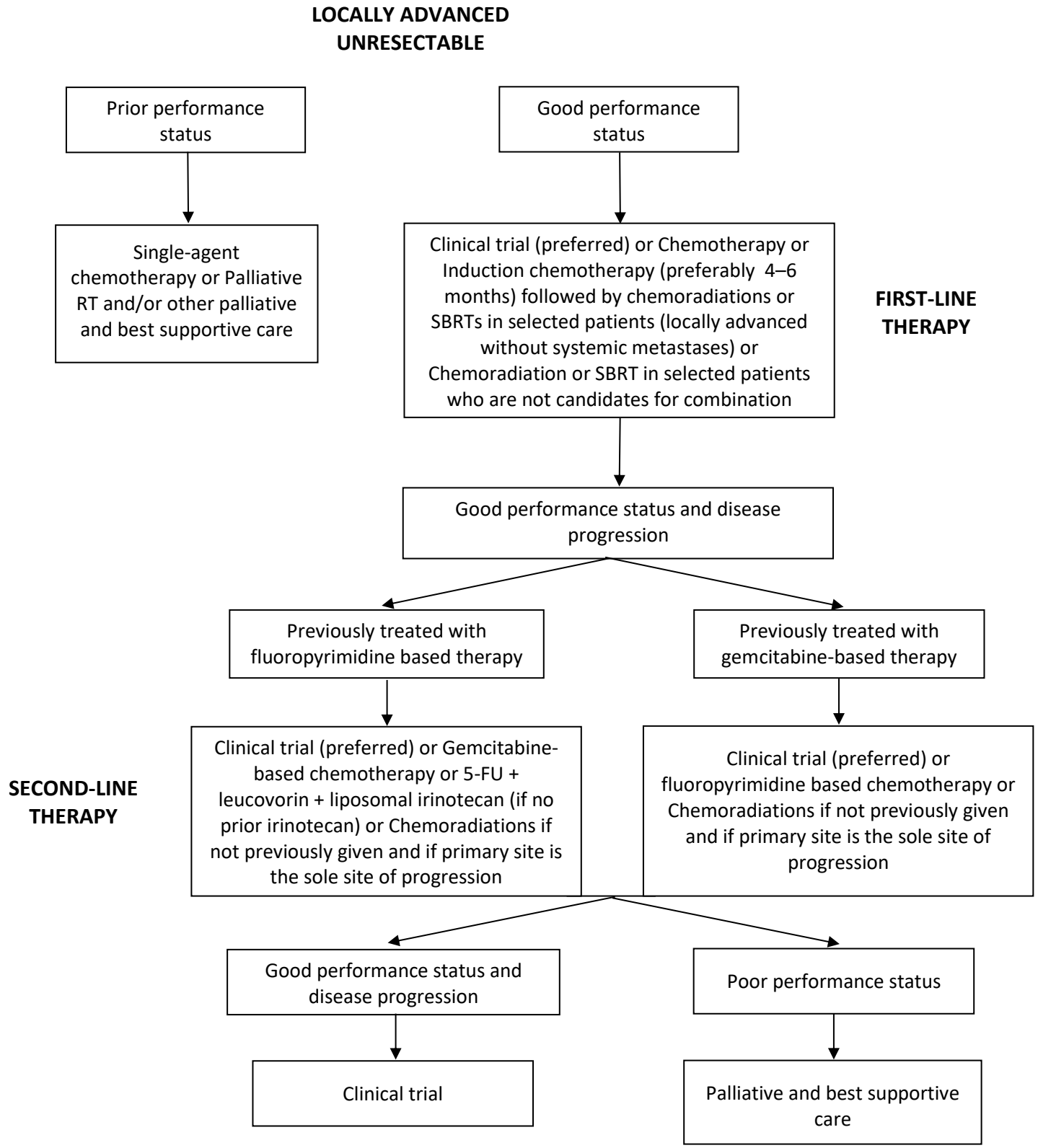

Table A8: Metastatic disease lines of treatment.

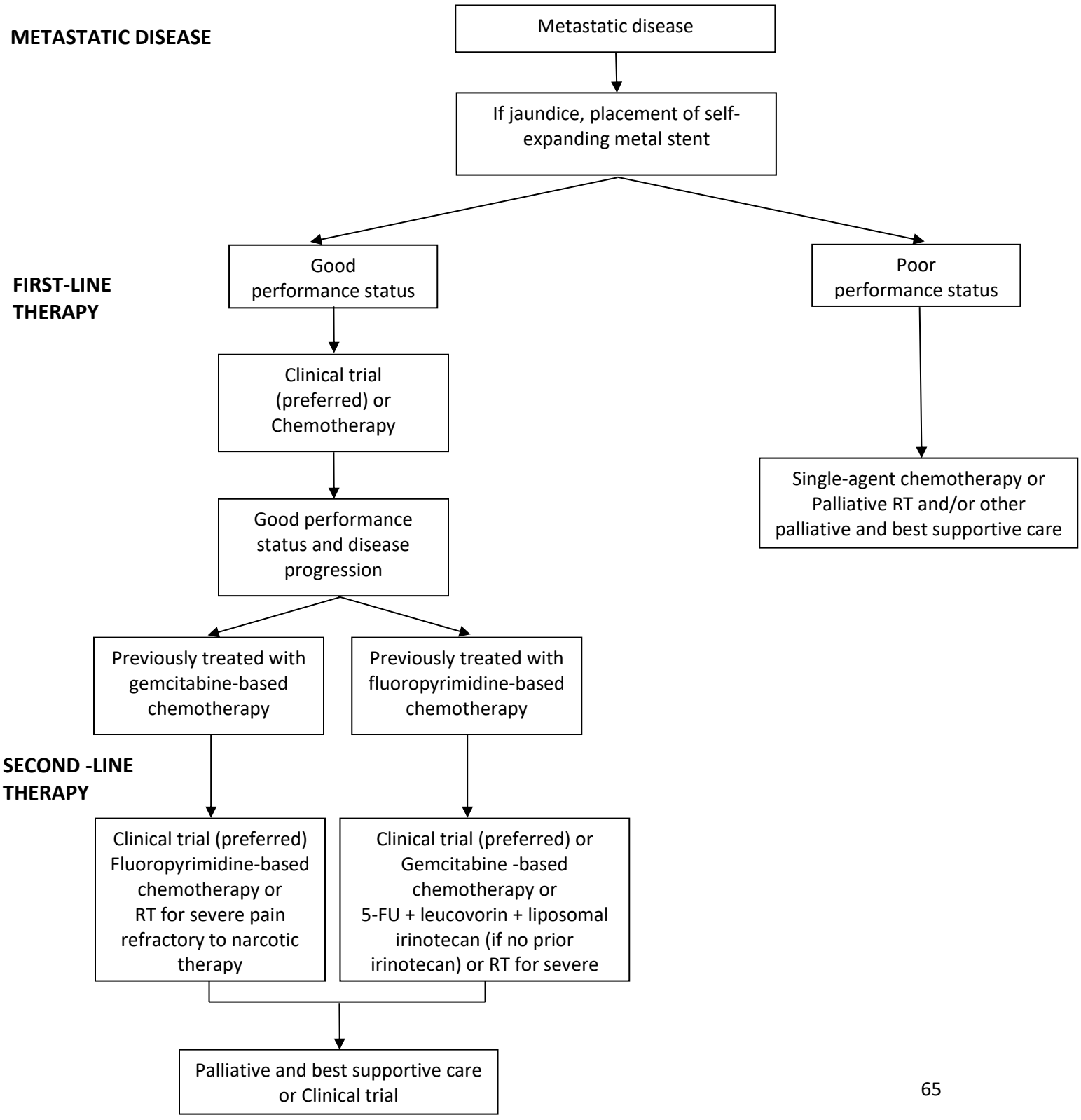

Table A9: Recurrence after resection treatment workup.

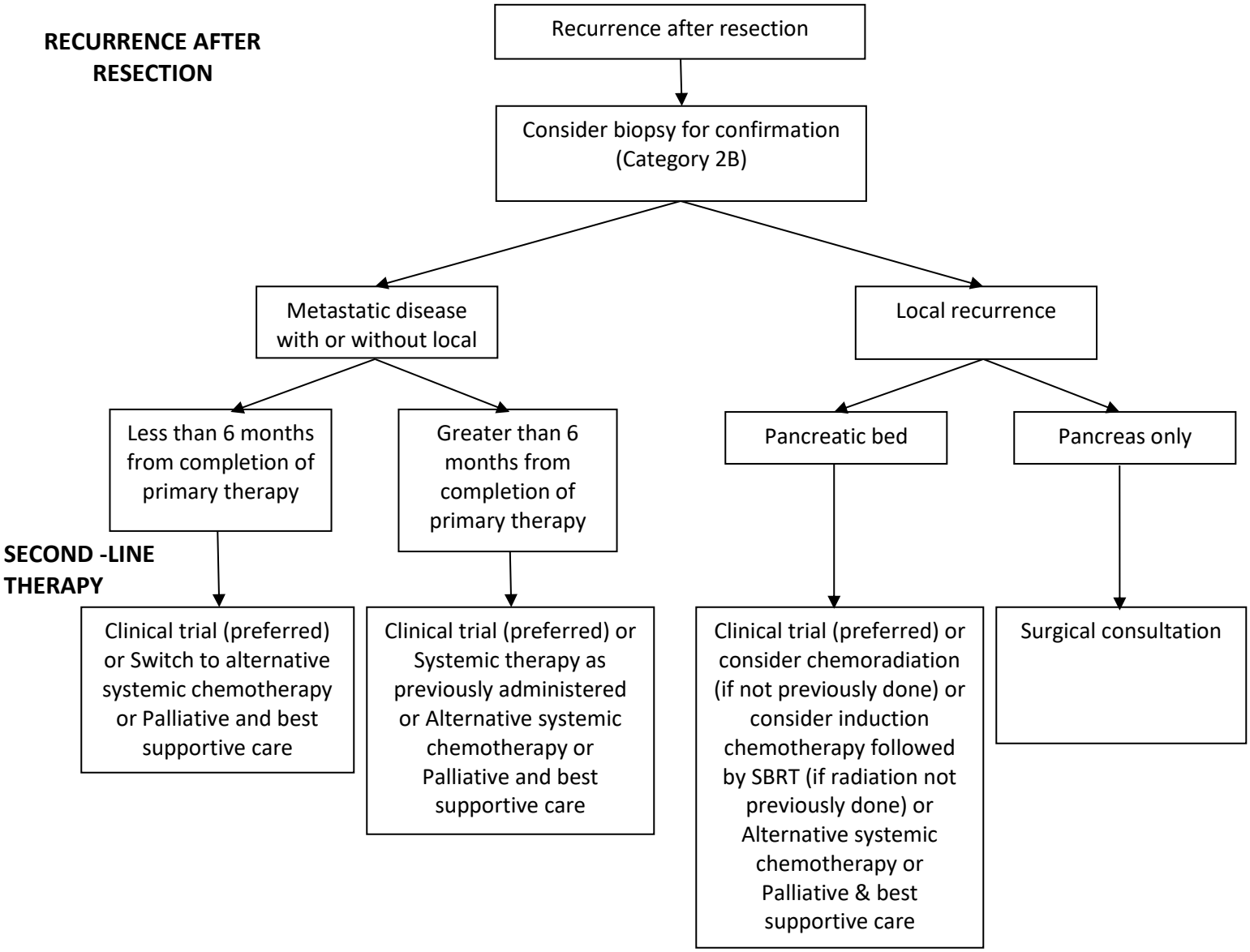

Table A10. Levels of evidence and grades of recommendation.

Levels of evidence I. Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity II. Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality or meta-analyses of such trials or of trials with demonstrated heterogeneity III. Prospective cohort studies IV. Retrospective cohort studies or case-control studies V. Studies without control group, care reports, expert opinions
Grades of recommendation A. Strong evidence for efficacy with a substantial clinical benefit, strongly recommended B. Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended C. Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ……), optional D. Moderate evidence against efficacy or for adverse outcome, generally not recommended E. Strong evidence against efficacy or for adverse outcome, never recommended

From Ref #1.