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"Shades of Gray" in pancreatic ductal adenocarcinoma: Reappraisals on resectability criteria
Debated indications for surgery in pancreatic cancer

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ABSTRACT

Pancreatic ductal adenocarcinoma is one of the leading causes of cancer-related deaths and, currently, surgery is the only curative treatment. Patients with borderline resectable pancreatic cancer (BRPC) can benefit from a multidisciplinary approach and R0 resection, and can achieve the same outcome as resectable patients treated with upfront surgery. However, the definition of BRPC changes according to different classifications with a heterogeneous distribution of patients, and it is thus difficult to compare clinical evidence. We performed a literature review to assess the most suitable classification of BRPC.

Our review was conducted using the PubMed database. Only articles containing more than ten patients classified according to NCCN, MDACC or AHPBA/SSAT/SSO classifications were selected.

A total of 16 studies were included in our analysis, and were grouped according to one of these three classifications. The total resection rate was 61.4%, with considerable differences between the groups (68.4% for NCCN, 54.9% for MDACC and 53.2% for AHPBA/SSO/SSAT). The total R0 resection rate was 90.1% (89.1% for NCCN, 92.5% for MDACC and 84% for AHPBA/SSO/SSAT). Of the three classifications, NCCN limits the use of confusing terms and uses restrictive criteria to define the most appropriate treatment for each subgroup. However, several reports have suggested that, even in the case of a limited disease, biological and clinical factors should be considered in order to classify patients as resectable.

NCCN classification appears to be the classification that allows the highest percentage of patients with BRPC to achieve resection without reducing the R0 resection rate. The choice of therapy should not only be based on imaging results, but also on a wider clinical multidisciplinary evaluation.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the third cause of cancer death worldwide. It is estimated that there will be 55,440 new cases in the USA in 2018 with 43,330 deaths. PDAC is associated with a very poor prognosis with a 5-year overall survival of 6%, when all stages are considered (Global Burden of Disease Cancer et al., 2015).

A surgical approach represents the only chance for curative treatment, although only approximately 10–15% of all cases of PDAC are resectable at diagnosis (Coveler et al., 2016; Li et al., 2004). Resectable PDAC is defined by both the absence of distant metastasis and the absence of local tumor extension to the celiac axis, superior mesenteric and common hepatic arteries, as well as the involvement $\leq 180^{\circ}$ of the superior mesenteric vein (SMV) or portal vein (PV) (Tempero et al., 2014).

Current evidence supports the importance of radical surgery; despite a recent meta-analysis which showed that R0/R1 rates vary according to the protocols of margin assessment and the pathological R0 definitions used (Chandrasegaram et al., 2015), several reports have demonstrated

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that patients who undergo excision with histologically positive margins (R1 resection) have a shorter overall survival (OS) compared to patients with negative margins (R0), and residual gross tumor (R2) resection cannot ensure a better prognosis than palliative treatment (Kim et al., 2016; Neoptolemos et al., 2001; Winter et al., 2006). Therefore, surgeons should avoid non-radical interventions that may only expose patients to possible complications without any benefit in survival.

Improvements in surgical techniques and perioperative care have shown the feasibility of pancreatoduodenectomy (PD), even in the presence of vascular invasion, provided that vascular resection is achievable (Leach et al., 1998). In recent years, several studies have demonstrated the superiority of this approach in terms of OS compared to palliative care alone, underlining the importance of accurate staging at diagnosis and consequent definition of the therapeutic strategy (Leach et al., 1998; Tseng et al., 2018).

For this purpose, a redefinition of resection concepts is essential in order to establish a clear boundary between “borderline resectable” and “locally advanced” disease.

2. Borderline resectability – classification and critical issues

Borderline resectable pancreatic cancers (BRPC) account for approximately 20% of locally advanced PDCA. BRPC is a localized, non-metastatic disease, in which surgery is technically feasible but with a high risk of positive margin due to vascular infiltration and, consequently, poorer prognosis (Al-Hawary et al., 2014; Katz et al., 2013; Varadhachary et al., 2006). In addition to anatomical issues, BRPC may also constitute a more biologically-aggressive disease that may not benefit from upfront surgery (Petrelli et al., 2015).

Several markers such as high Ca19.9, a tumor size of > 3 cm, inflammatory parameters defined by a high Glasgow score, and poor differentiation predict early disease recurrence after radical surgery (Barugola et al., 2007a, 2007b;Hartwig et al., 2013a, 2013b; La Torre et al., 2012b; Matsumoto et al., 2015a; Reid-Lombardo et al., 2013b; Tzeng et al., 2014a, 2014b). These markers have been validated in resectable PDCA, but their application in BRPC can also be relevant. Molecular prognostic factors such as SMAD4, CXCR4, SOX9, IFIT3 or stromal SPARC in the diagnostic specimen could predict early disease recurrence and the presence of micrometastases. (Popp et al., 2017; Yamada et al., 2015). However, these molecular factors are still undergoing investigation and their use in current practice is not straightforward.

Based on these assumptions, and due to the lack of validated biological criteria to discriminate against low or high biological risks, it seems reasonable to consider the use of neoadjuvant chemotherapy to increase the R0 resection rate and, consequently, the survival of all BRPC patients.

Currently, the use of neoadjuvant therapy for non-metastatic PDAC has not been standardized or included into any clinical guidelines with a high level of evidence. Five meta-analyses, which only considered resectable PDAC compared to non-resectable disease, failed to demonstrate an advantage for upfront chemotherapy or chemoradiotherapy followed by surgery (Andriulli et al., 2012; Assifi et al., 2011; Gillen et al., 2010; Laurence et al., 2011; Xu et al., 2014). However, the non-resectable PDAC group included both BRPC and unresectable localized tumors.

Due to the identification of BRPC, locally advanced non-metastatic disease is more correctly divided into two different entities, namely those patients who would achieve the same results as resectable PDAC, and those who should be treated as unresectable.

Tang et al. (Tang et al., 2016) observed that when BRPC patients were considered separately from patients with non-resectable disease, the percentage of patients who underwent surgery after upfront chemotherapy was higher than in unresectable patients (63.0% vs 32.8%), and was equivalent to that of resectable patients (75.5%), as described by previous studies (Gillen et al., 2010). Moreover, the BRPC R0 resection rate was reported to be comparable to resectable patients, and patients with BRPC who underwent surgery after chemotherapy had a similar OS to upfront resectable patients (25.9 months, range: 21.1–30.7 months) (Andriulli et al., 2012; Assifi et al., 2011; Gillen et al., 2010; Laurence et al., 2011).

These outcomes were achieved even though after neoadjuvant chemotherapy a partial response (PR) was observed in less than one third of patients with BRPC, whereas the majority displayed stable disease (SD). These data suggest that the objective response after upfront chemotherapy is not an appropriate endpoint to evaluate disease resectability. This may be related to several reasons: firstly, the desmoplastic reaction that typically surrounds PDAC does not shrink, leading to an overestimation of the tumor dimensions. Secondly, therapy induces regional changes, such as pancreatitis, which may result in a difficult assessment of the local extension of the tumor (Balthazar et al., 2005). Finally, the response to systemic or local therapies consists in evaluating the replacement of viable tissue by fibrosis, which cannot be distinguished by computed tomography (CT) (Tamm et al., 2006; White et al., 2001).

Therefore, preoperative classifications are crucially important because they are based on vascular involvement rather than dimensional assessments.

The first definition of BRPC was published by the National Comprehensive Cancer Network (NCCN) in 2009, and subsequent updates have been published over the years. In addition, several other definitions from different institutions have been reported.

The meta-analysis by Gillen et al. (Gillen et al., 2010) evaluated 111 studies of neoadjuvant therapy in non-metastatic PDAC. Of these studies, seven (6.3%) used the NCCN guidelines of resectability. A total of 45 studies (40.5%) clearly defined resectability according to vascular involvement or maximal tumor dimensions. In the remaining 59 studies (53.2%), resectability criteria were not clearly stated (for example, they were evaluated by a single surgeon or an interdisciplinary team) or not stated at all.

Describing in detail the different classifications previously reported goes beyond the scope of this review. Instead, we focus on the classifications that have gained more consensus as they have tried to standardize the definition of borderline resectability, thus overcoming the widespread use of local classifications; 1) NCCN classification; 2) MDACC (MD Anderson Cancer Centre) classification and 3) The Americans Hepatopancreatobiliary Association (AHPBA)/Society for Surgery of the Alimentary Tract (SSAT)/Society of Surgical Oncology (SSO) classification. Their definitions are summarized in Table 1.

At a first glance, these classifications are very similar to each other. However, in most cases, the use of ambiguous and non-objective terms prevails. This also involves a certain degree of heterogeneity when different classifications are compared. In the study by Lee et al. (Lee

Table 1
Principal BRPC classification and radiological differences. CA: Celiac artery, CHA: common hepatic artery, SMA: superior mesenteric artery, SMV/PV: superior mesenteric vein/portal vein.

Involved vessel	NCCN 2012	MDACC	AHPBA/SSAT/SSO
CA	No abutment or encasement	Abutment	No abutment or encasement
CHA	Abutment or short segment encasement	Abutment or short segment encasement	Short-segment abutment or encasement amenable to reconstruction
SMA	Abutment	Abutment < 180	Abutment < 180
SMV/PV	Abutment with impingement or narrowing	Short-segment occlusion amenable to resection and reconstruction	Abutment > 180 or occlusion amenable to resection and reconstruction

Table 2
NCCN classification v2.2016 of BRPC.

Involved vessel	
CA	Contact 180°
CHA	Contact without extension to celiac axis or hepatic artery bifurcation amenable to resection and reconstruction
SMA	Contact 180°
SMV/PV	Contact of > 180°; contact of 180° with irregularity of veins or thrombosis amenable to resection and reconstruction

et al., 2012), 43 patients with unresectable PDAC were classified according to two different criteria. When the Asian Pancreatobiliary Cancer Center (APBCC) criteria were used, 33 patients were classified as BRPC, but when the NCCN criteria were applied to the same patients, only 18 patients were included in the BRPC group.

Similarly, Denbo et al. (Denbo and Fleming, 2016) classified 129 patients according to both AHPBA and MDACC definitions. According to AHPBA criteria, 122 patients were considered having BRPC, and seven were considered unresectable. However, only 77 patients were considered as having BRPC (and 52 were potentially resectable) using MDACC criteria.

Therefore, in 2009, the American Hepato-Pancreato-Biliary Association (AHPBA) expanded the venous involvement criteria to include tumor abutment of the superior mesenteric vein/portal vein with or without impingement and narrowing of the lumen (Vauthey and Dixon, 2009).

In 2013, the Alliance for Clinical Trials in Oncology was assigned the aim of clearly defining BRPC by reproducible means (Katz et al., 2013) and allowing uniform enrolment of patients into multi-institutional trials in this setting.

A recent investigation has carried out with the latest version of the NCCN classification (Table 2). The milestones of the NCCN panel over time, compared to other classifications, are to limit the use of terms that can be confusing and to adopt restrictive criteria to prevent understaging and an incorrect therapeutic approach (Tempero et al., 2014).

The major advantage of this classification is eliminating and replacing confusing terms with a clear and reproducible terminology thanks to measurable criteria. These features and their applicability have brought international institutions, such as the International Study Group of Pancreatic Surgery (ISGPS), to support the NCCN classification (Bockhorn et al., 2014).

Studies from MDACC have recently produced a new classification of BRPC that has a more holistic view, namely clinical conditions that make patients fit for surgery, biological staging, and resectability criteria are taken into account (Denbo and Fleming, 2016). Biological staging includes both Ca19.9 levels and likelihood of distant metastasis. Using these parameters, it is more probable that patients are identified who can receive upfront surgery and those who have a biologically aggressive disease that will never benefit from resection.

Moreover, it seems that this classification could be relevant not only in BRPC but also in patients with resectable disease; approximately 20% of patients experience progressive disease during neo-adjuvant therapy, regardless of having resectable upfront, or BRPC, or non-resectable tumors (Gillen et al., 2010; Tang et al., 2016). We can assume that, despite the initial presentation, these tumors have an aggressive biology that predicts an unfavorable prognosis. These patients probably need to receive the same therapeutic strategy as if they had unresectable disease.

3. Literature review

The literature review was conducted via a Medline search using the key words “pancreas” or “pancreatic”, combined with “cancer” or “carcinoma” or “adenocarcinoma” or “tumor” or “neoplasm” and “surgery” or “borderline resectable” or “locally advanced”. Only articles written in English and containing more than ten patients classified according to NCCN, MDACC or AHPBA/SSAT/SSO classifications were selected for this review.

4. Classifications and surgery: study results

We selected 16 studies in which patients with BRPC were included (Table 3) (Blazer et al., 2015; Boone et al., 2013; Chakraborty et al., 2012; Christians et al., 2014; Katz et al., 2012; Katz et al., 2008; Lee et al., 2012; Leone et al., 2013; Motoi et al., 2014; Nanda et al., 2015; Paniccia et al., 2014; Rashid et al., 2016; Rose et al., 2014; Stokes et al., 2011; Takahashi and Akita, 2015; Tseng et al., 2018). Ten studies included only BRPC and six studies also included both resectable and locally advanced, non-metastatic cancer. We only evaluated studies where the selection criteria of BRPC were easily recognizable and belonged to one of the major considered classifications. We then divided the studies into three different subgroups based on the different classifications.

These studies covered a broad period, including patients treated between 1999 and 2013. Overall, the 16 reviewed trials included 1148 patients. Seven studies had more than 50 patients and six studies had more than 100 patients.

Data collected included demographics, tumor localization, Performance status (PS), median baseline Ca19.9 and toxicity (Table 4).

Table 3
Characteristics of selected studies included in the review.

NCCN classification	Type of study	Period	Cases (numbers)	Patients resected (%)	R0 resected (%)
Lee et al	Single institution retrospective	2006-2008	18	11(61%)	9 (82%)
Leone et al.	Prospective	2003-2009	15	9 (60%)	8 (88.9%)
Motoi et al.	Single institution retrospective	2007-2009	203	158 (77.8%)	123 (77.8%)
Nanda et al.	Single institution retrospective	2010-2013	14	10 (71.4%)	–
Paniccia et al.	Single institution retrospective	2011-2013	31	17 (54.8%)	17(100%)
Rashid et al.	Single institution retrospective	2006-2013	101	55(54.5%)	53 (96%)
Takahashi et al.	Single institution retrospective	2002-2013	184	127 (69%)	126 (99.2%)
MDACC classification					
Chakraborty et al.	Phase II	2010-2012	13	5 (38.5%)	4 (80%)
Christians et al.	Single institution retrospective	2010-2012	18	12 (66.6%)	12 (100%)
Katz et al. (2008)	Single institution retrospective	1999-2006	160	66 (41.2%)	62 (94%)
Katz et al. (2012)	Single institution retrospective	2005-2010	122	85 (69.6%)	81 (95.2%)
Stokes et al.	Single institution retrospective	2005-2008	34	16 (47)	12 (75%)
Tzeng et al.	Single institution retrospective	2001-2010	141	84 (59.6%)	77 (91.6%)
AHPBA/SSO/SSAT classification					
Blazer et al.	Single institution retrospective	2011-2013	18	11 (61%)	9 (82%)
Boone et al.	Single institution retrospective	2011-2012	12	8 (73%)	6 (55%)
J.B. Rose et al.	Phase II	2008-2012	64	31 (48.9%)	27(87%)

Table 4
Characteristics of patients included in the studies.

	Lee	Leone	Motoi	Nanda	Paniccia	Rashid	Taka -hashi	Chakra-borty
Age:	61	63	65	63	65	67	–	66
Median (range)	(42-76)	(43-75)	(32-87)	(48-77)	(58-68)	(45-87)		(51-82)
Sex (%)	58.1%	53.8%	59%	57%	55.6%	60.1%	61%	38%
Men	41.9%	46.2%	41%	43%	44.4%	39.9%	39%	62%
Women								
Tumor Localization (%):	60.5%	66.6%	NA	NA	66%	82.6%	81%	NA
Head/uncinate	39.5%	33.4%			44%	17.4%	19%	
Neck/Body								
Performance status:	NA	66.6%	NA	21.4%	50%	73.5%	NA	NA
0		30.8%		71.4%	50%	24.8%		
1		2.6%		7.2%	–	1.7%		
2								
Median baseline CA19-9:	266.7 (2.0-2520)	NA	203.75 (0–220)	230	NA	232 (1148)	NA	NA
n (range)				(2–1386)				
Neo-adjuvant	Gemcitabine	Gemcitabine-Oxaliplatin	Gemcitabine/	FOLFIRINOX	Gemcitabine/	Gemcitabine/	Gemcitabine	Capecitabine
chemotherapy:			S1/gemcitabine + S1		FOLFIRINOX	Docetaxel/ Capecitabine		
Neo-adjuvant radiotherapy	60	50.4	45	50.4	30	30-40	50	50.4
(Gy):								
Toxicity ≥G3 (%):	5%	0%	1.4%	0%	5.6%	NA	–	1%
-Anemia	21%	–	16.3%	0%	–		52%	–
-Leucopenia	33%	5.1%	33.8%	0%	5.6%		–	–
-Neutropenia	0%	–	–	0%	–		–	1%
-Bleeding	5%	5.1%	1.4%	0%	11.1%		–	0%
-Nausea	0%	7.6%	0%	0%	11.1%		–	0%
/vomiting	2%	0%	–	0%	–		–	0%
-Fatigue	5%	–	–	0%	16.7%		–	0%
-Diarrhea	2%%	–	0%	0%	5.6%		–	–
-Mucositis	11%	–	–	0%	–		–	0%
-Rash	-A	2.5%	-A	0%	22%		–	–
-HFS								
-Neurotoxicity								

	Chri -stians	Katz et al. (2008)	Katz et al. (2012)	Stokes	Tzeng	Boone	Blazer	J.B. Rose
Age:	59.8	63	65	66	63	59	62.2	66
Median (range)	(± 9.6)	(36-90)	(34-81)	(45-83)	(34-81)	(42-73)	(± 8.7)	(61-73)
Sex (%)	58.3%	52%		63%	47.5%	48%	61%	55%
Men	41.7%	48%		37%	52.5%	52%	39%	45%
Women								
Tumor Localization (%):	NA	89%	NA	90%	89.4%	NA	89%	NA
Head/uncinate		11%		10%	10.6%		11%	
Neck/Body								
Performance status:	NA	NA	NA	NA	NA	NA	PS 0-1: 100%	–
0								–
1								13%
2								
Median baseline CA19-9:	489.9 (49.1–5000)	212	218	228	274 (42–8662)	371	650.88	357 (100–999)
n (range)		(2.3–11,482)	(11-4546)	(< 1-13013)		(8–19,000)	(≤15–10944)	
	FOLFIRINOX			Capecitabine		FOLFIRINOX	FOLFIRINOX	

(*continued on next page*)

Table 4 (*continued*)

	Chri -stians	Katz et al. (2008)	Katz et al. (2012)	Stokes	Tzeng	Boone	Blazer	J.B. Rose
Neo-adjuvant chemotherapy:		5-Fluorouracil/ Paclitaxel/ Gemcitabine	Gemcitabine/ 5-Fluorouracil/ Capecitabine		Gemcitabine/ 5-Fluorouracil			Gemcitabine/ Docetaxel
Neo-adjuvant radiotherapy (Gy):	50.4	50.4	50.4	50.4	–	–	30	50.4
Toxicity ≥ G3 (%):	–	NA	NA	–	NA	–	–	NA
-Anemia	–					–	–	
-Leucopenia	14.3%					15%	0	
-Neutropenia	–					–	–	
-Bleeding	NA					–	4.7%	
-Nausea	35.7%					–	9.3%	
/vomiting	14.3%					5%	14.0%	
-Fatigue	–					–	0%	
-Diarrhea	–					–	0%	
-Mucositis	–					–	–	
-Rash	–					–	0%	
-HFS								
-Neurotoxicity								

NA, Not available. HFS, Hand-foot Syndrome.

In 13 studies, these data were clearly defined for BRPC patients, but in three studies, BRPC and locally-advanced unresectable cancer were analyzed without distinction. Progression-free survival (PFS) and OS were not analyzed because these last studies did not distinguish these outcomes between BRPC and unresectable cancer.

However, the population in these studies was reasonably homogeneous. The median age in these studies ranged between 59 and 67 years, with a greater incidence in the male population. Almost all patients had PS 0 or 1. In all studies, neoadjuvant chemotherapy was either used in the form of monotherapy (gemcitabine or capecitabine) or in combination with other treatments (FOLFIRINOX or capecitabine/ gemcitabine with other cytotoxic therapies). Most patients were treated with Gemcitabine- or 5-Fluorouracil-containing doublet and only five studies, which recruited 82 patients, used FOLFIRINOX as the chosen schedule.

We analyzed the results of each trial and focused our attention on the resection rate and R0 resection rate. These outcomes are clearly defined for BRPC, and we assumed they were the most suitable and unbiased outcome measures. We then calculated the results for the total number of patients as a unique population according to the three classifications taken into account.

Globally, 705 BRPC patients (61.4%) enrolled in the studies underwent resection, and among them 626 (90.1%) achieved an R0 resection.

According to the three classifications, resection was achieved in 387/566 patients (68.4%) in the NCCN group, in 268/488 patients (54.9%) in the MDACC group and in 50/94 patients (53.2%) in the AHPBA/SSO/SSAT group.

R0 resection was reached in 336/377 patients (89.1%) for the NCCN group, in 248/268 patients (92.5%) for the MDACC group and in 42/50 patients (84%) for the AHPBA/SSO/SSAT group.

5. Expert opinion

The primary objective of surgery for pancreatic cancer is complete removal of the tumor with negative resection margins to reduce the risk of local relapse. At the time of diagnosis, only 20% of patients with pancreatic cancer are surgically resectable. In addition, pancreatic surgery involves a high operatory risk, which makes necessary to carefully select patients.

It is therefore crucial to accurately stage patients before surgery in order to identify the best treatment strategy according to the extension of the disease. Indeed, a clear differentiation between resectable and unresectable patients is essential to allow R0 resection to be achieved, which potentially cures patients.

While there is a major degree of consensus on the definitions of resectable and unresectable pancreatic cancer in the literature and international guidelines, BRPC remains a debated issue.

Indeed, the outcomes of treatment intervention change when eligibility for surgery changes and the criteria of resectability become critically important. The guidelines advocated by the AHPBA/SSO/SSAT, MDACC and NCCN have also been widely used in clinical studies and we focused our analyses on these classifications, which have gained more consensus trying to overcome local classifications that make BRPC a non-standardized issue.

Considering both clinical and scientific relevance, and based on the review of pertinent literature, it would be advisable, in our opinion, to adopt the resectability criteria produced by NCCN (Table 2) as a reference. These guidelines propose “semantic” and “conceptual” simplification, eliminating countless, misleading definitions such as distortions, narrowing, abutment, impingement and encasement that were used in previous classifications.

Moreover, it is important to correctly identify patients with “borderline resectable disease” clearly from the beginning and in a uniform way, in order to avoid both over- and under- treatment.

Comparing the outcome of patients included in the studies, which

are heterogeneous, based on the different classifications, and could thus prove difficult. In addition, other limitations should be noted, for example, the type of study and sample size, the use of radiotherapy and the different neo-adjuvant chemotherapy schedules. However, these factors highlight the heterogeneity of the studies in this setting.

Nevertheless, considering the strong focus on resectability pursued by the different classifications we analyzed, we can determine that the NCCN classification appears to be the preoperative classification that allows the highest percentage of patients to achieve resection without reducing the R0 resection rate.

Currently, the contrast enhanced multi detector CT scan remains the imaging of reference for preoperative resectability assessment. MRI could have the same role, adding useful topographic information on biliary extension in the case of differential diagnosis with suspected distal bile duct neoplasia. Endoscopic Ultra-Sonography (EUS) with fine needle aspiration biopsy (FNA) has a complementary role for further staging confirmation; in addition, it is essential to provide histological sampling that can be required for differential diagnosis with other pancreatic masses (autoimmune pancreatitis, chronic pancreatitis, lymphoma, etc.) or when neoadjuvant treatment is planned.

The decision on the resectability status in PDAC must always be taken during a multidisciplinary meeting, with at least one dedicated radiologist, an oncologist and a pancreatic surgeon to evaluate the extension of the disease and set the individualized therapeutic algorithm. Once resectability is defined from radiological images, the multidisciplinary evaluation should consider the entire clinical picture of the patient (age, symptoms, associated comorbidities, PS) to contextualize the therapeutic choice for every single case, with maximum refining of the indications for upfront surgery.

Furthermore, a wider evaluation should also consider the biological behavior of the disease at diagnosis, including CA19-9 levels, duration of the symptoms, tumor diameter and grading, and the Glasgow prognostic index (Barugola et al., 2007a, 2007b;Hartwig et al., 2013a, 2013b La Torre et al., 2012a; Matsumoto et al., 2015b; Reid-Lombardo et al., 2013a; Tzeng et al., 2014a, 2014b).

The integration of resectability objective criteria associated with poor prognostic “biological criteria” allows the selection of a well-defined population of potentially resectable patients who should be offered preoperative treatment. However, the lack of conclusive evidence on these markers prevents the creation of a mixed classification with biological and anatomical criteria. Therefore, the most effective chemotherapy combinations that are approved for metastatic disease can be exploited to maximize the outcome of neoadjuvant treatment in this setting.

The response evaluation after neoadjuvant chemotherapy must be followed through radiologic restaging using the same method as that carried out for diagnosis; comparisons should be subordinate to “Response Evaluation Criteria in Solid Tumors”, as well as to clinical (variation in performance status) and biological assessments (Ca 19-9 levels). Indeed, in uncertain cases of patients with tumors of a diameter of > 3 cm and elevated CA 19-9 levels, explorative laparoscopy alone or with intraoperative ultrasonography (IOUS) should be considered, in order to avoid useless laparotomy and to highlight peritoneal carcinomatosis or small metastasis undetected by CT scanning.

In conclusion, to date, a careful preoperative radiological classification may help in defining subgroups of patients and orient them to the most appropriate treatment depending on the stage of disease and the clinical context. Nevertheless, radiological classifications can be inaccurate, and biological criteria should be integrated into anatomic classifications in order to avoid both useless surgery with a high morbidity risk, and to maximize efforts into ensuring that potentially operable patients are given surgery.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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