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Progress Report

Borderline resectable pancreatic cancer: More than an anatomical concept

Fausto Petrelli[a,*], Alessandro Inno[b], Sandro Barni[a], Antonio Ghidini[c], Roberto Labianca[d], Massimo Falconi[e], Michele Reni[f], Stefano Cascinu[g], on behalf of GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente) and San Raffaele Hospital

[a] Medical Oncology Unit, ASST Bergamo Ovest, Bergamo, Italy
[b] Medical Oncology Unit, Sacro Cuore Don Calabria Hospital, Verona, Italy
[c] Medical Oncology Unit, Casa di Cura Igea, Milano, Italy
[d] Medical Oncology Unit, ASST Papa Giovanni XXIII Hospital, Bergamo, Italy
[e] Surgical Department of Pancreas, San Raffaele Hospital, IRCCS, Milano, Italy
[f] Medical Oncology Unit, San Raffaele Hospital, IRCCS, Milano, Italy
[g] Department of Oncology and Hematology, University of Modena and Reggio Emilia, Modena, Italy

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ABSTRACT

Borderline resectable pancreatic cancer (BRPC) accounts for about 10–15% of newly diagnosed pancreatic cancer, and its management requires a skilled multidisciplinary team. The main definition of BRPC refers to resectability, but also a high risk of positive surgical margins and recurrence. This raises questions about the value of surgery and suggests an opportunity to utilize preoperative treatment in this subset of patients.

Besides technical borderline resectable disease which is defined on anatomical and radiological criteria, there is also a biological borderline resectable disease which is defined on clinical and biological prognostic factors. Technical borderline resectable disease requires tumor shrinkage with aggressive therapy including modern drug combinations +/− radiotherapy to achieve radical surgery. Biological BRPC needs always an early systemic treatment in order to select the best candidates for subsequent radical surgery. It is important to distinguish between these different clinical scenarios, both in clinical practice and for clinical trials design.

1. Introduction

The definition of borderline resectable pancreatic cancer (BRPC) is a much debated issue. Several different versions have been proposed over the years, all of them based on the extent of vessel involvement (venous and arterial) by the tumor. The main definition of BRPC refers to a concept of technical resectability, but also a high risk of positive surgical margins and recurrence [1–5]. This raises questions about the real value of surgery and suggests an opportunity to utilize preoperative treatment in this subset of patients. However, given that around 60% of patients undergoing radical surgery die within 18–24 months of the procedure, it is easy to acknowledge that upfront surgery is the best treatment approach for only a minority of patients.

This leads to the substantial need to expand the concept of what is a borderline resectable tumor. In reality, along with the one feature that is classically identified by anatomical definition criteria, some other clinical, pathological, and biological features may help us to identify resectable patients who would not benefit from surgery. In other words, borderline resectable tumors could be divided into two different entities:

- Technical borderline: tumors involving vessels to a limited extent and for which resection would likely be compromised by positive surgical margins (Table 1).
- Biological borderline: tumors that, despite technical resectability, have an unfavorable biology that leads to an early relapse or death.

Both technical and biological borderline resectable tumors should require systemic treatment before surgery, albeit with different aims.

* Corresponding author at: Medical Oncology Unit, ASST Bergamo Ovest, Piazzale Ospedale 1, 24047 Treviglio, Bergamo, Italy. Fax: +39 0363424380.
E-mail address: faupe@libero.it (F. Petrelli).

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Table 1
Ongoing neoadjuvant trials in borderline resectable and resectable pancreatic cancer.

Type of study	NCT	Country	Stage of disease	Neoadjuvant arms	Radiotherapy	Surgery	Primary endpoint
Randomized phase 2	NCT02241551	US	BRPC	GEM + NAB-P vs FOLFIRINOX	SBRT if BRPC after CT	Yes after SBRT	pCR, R0 resections, G4 tox
Randomized phase 2	NCT02676349	France	BRPC	mFOLFIRINOX vs mFOLFIRINOX → CTRT	CTRT with X in arm B	Yes	R0 resection
Phase 2	NCT01897454	US	BRPC	FOLFIRINOX x4	CTRT with GEM	Yes	R0 resection
Phase 2	NCT01661088	US	BRPC	FOLFIRINOX x6	IMRT with GEM	Yes	R0 resection
Phase 2	NCT01591733	US	BRPC	FOLFIRINOX x4	RT short course with X	Yes	R0 resection
Phase 2	NCT02427841	US	BRPC	GEM + NAB-P	CTRT with 5FU	Yes	R0 resection
Randomized phase 2	NCT02839343	US	BRPC	FOLFIRINOX vs FOLFIRINOX→ RT	Hypophractionated RT	Yes	OS at 18 months
Randomized phase 2	NCT02125136	German	LAPC	FOLFIRINOX x4 vs GEM + NAB-P x4	–	Yes in no PD	Conversion rate
Phase 2	NCT02723331	US	Resectable and BRPC	GEM + NAB-P	SBRT	Yes	R0 resection
Randomized phase 2–3	NCT02172976	German	Resectable	Neoadj + adj FOLFIROX vs adj GEM	–	Yes	OS
Phase 3	NCT01900327	German	Resectable	GEM + RT vs surgery	CTRT with GEM	Yes	3 year OS

CTRT, chemoradiotherapy; pCR, pathologic complete response; BRPC, borderline resectable pancreatic cancer; LAPC, locally advanced pancreatic cancer; CT, chemotherapy; IMRT, intensity-modulated radiotherapy; tox, toxicity; R0, radical resection; US, United States; RT, radiotherapy; SBRT, stereotactic body radiotherapy; neoadj, neoadjuvant; adj, adjuvant; GEM + NAB-P, gemcitabine + nab paclitaxel; FOLFIRINOX, 5-Fluorouracil + folinic acid + oxaliplatin + irinotecan; X, capecitabine.

2. Technical borderline disease

There is no standard form of care for borderline resectable tumors. The efficacy of systemic therapy for pancreatic cancer has improved moderately over the years, with modern agents and combinations [namely 5-Fluorouracil plus oxaliplatin and irinotecan (FOLFIRINOX) and gemcitabine plus nab-paclitaxel] replacing gemcitabine alone as the standard care for fit patients with metastatic disease. Unfortunately, only patients with metastatic disease were enrolled in the phase 3 trials involving FOLFIRINOX and gemcitabine plus nab-paclitaxel [6,7], meaning that the results cannot be directly applied in the locally-advanced setting. However, modern combination regimens have been demonstrated to improve not only progression-free (PFS) and overall survival (OS), but also the response rate when compared to single-agent gemcitabine [8]. Accordingly, these results suggest that chemotherapeutic regimens such as FOLFIRINOX or Nab-paclitaxel/gemcitabine may play a crucial role in the treatment of technically borderline resectable tumors, as they have a greater likelihood of leading to their downsizing.

Only a few studies have addressed resection rates and responses after neoadjuvant chemotherapy (CT) in BRPC. These were brought together in a systematic review and meta-analysis by Tang et al. in 2016 [9]. They identified 18 studies encompassing about 1000 patients, and evaluated responses, resection rates, and outcomes of BRPC. Overall, the pooled response rate was 30%, with a resection rate of 65% and R0 resections of 57% (87% of all resected tumors). The outcome in terms of OS for resected patients was double that of non-resected cases (25.9 vs 11.9 months). FOLFIRINOX-based regimens were found to be associated with a 72% resection rate compared to 67% for gemcitabine-based CT. This confirms a previous meta-analysis of FOLFIRINOX as a neoadjuvant regimen for locally-advanced pancreatic cancer [10]. Among borderline resectable disease, the pooled resection rate was 68.5% and the rate of R0 resection 93%. Therefore, in fit patients able to tolerate triplet-based CT, FOLFIRINOX seems to be a worthy combination, while a gemcitabine doublet can be a good compromise in other cases. In both situations, the median survival for resected patients was similar to that of those with resectable cancer. Anyway, the choice of regimen such FOLFIRINOX is not easy and not for all patients because of the toxicity related to the treatment: myelosuppression and neuropathy in fact are side effects that can hamper subsequent therapies in the history of disease.

3. Biological borderline disease

A tumor considered resectable based only on its anatomic extent may have high risk of early relapse after surgery, due to its intrinsic biological features. This is what we define as biologically borderline pancreatic cancer. For these individuals, the aims of neoadjuvant therapy are to: select the best patients for radical surgery; avoid putting those through surgery who will go on to rapidly develop progressive disease; and treat earlier the micrometastases that can emerge after surgery [11]. In fact, accumulating preclinical evidence demonstrate that the seeding of pancreatic cancer cells in distant organs often occurs even before tumor formation at the primary site [12]. This early metastatic spread is the responsible for relapse and death, thus providing a rationale for the use of upfront systemic therapy for most patients who present with a so called “early stage” disease [13]. The ability of detecting micrometastases at the time of diagnosis would be useful for tailoring neoadjuvant treatment in this setting. Several innovative molecular-based imaging techniques have demonstrated to detect pre-invasive pancreatic cancer in preclinical models [14–16], and they possibly worth further development as a diagnostic tool for pancreatic can-