Editorial

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In search of evidence – PIPAC on the fast lane

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Further randomized studies are needed … is arguably the most frequent conclusion of publications in the field of oncological surgery and most of the time also a hopeless prayer. High-level evidence is indeed always welcome. However, it is a tremendous challenge to conduct randomized controlled trials (RCT) in cancer surgery. Heterogeneity of patients and treatments, difficult blinding, and modest sample size are just some out of many methodological shortcomings frequently encountered in surgical RCTs. Moreover, it is difficult to fund RCTs in surgical oncology since there is usually no major industrial support, in contrast to medical oncology. Last but not least, if the available evidence suggests a much worse outcome for the control arm vs. the experimental surgical arm, it can be very challenging or even impossible to recruit enough patients for a randomized trial.

Therefore, it is all but a surprise that most current practice in surgery is not supported by level-I evidence. Prominent examples are laparoscopic vs. open cholecystectomy, hepatectomy for liver metastases, cytoreductive surgery (CRS) in ovarian cancer and the Whipple's procedure in pancreatic cancer – as compared to systemic palliative chemotherapy. This has led some authors to ignore all evidence except double-blinded RCTs and to compare surgical research with a *comic opera* [1] – which might appear inappropriate considering the challenges above. Prominent authors suggest therefore that large-scale prospective multicenter data might fill the evidence gap in surgical oncology research [2]. But still, only high-quality evidence – ideally in the form of RCTs – will persuade the different stakeholders to accept a novel treatment and the health insurances to pay for it [3].

CRS and Hyperthermic IntraPEritoneal Chemotherapy (HIPEC) might serve as an example for the difficulties encountered in evidencing an innovative surgical procedure. The concept of CRS and HIPEC is more than 30 years old, but results from the first RCT were reported only after 15 years: a Dutch multicenter study showed a significant survival benefit for patients with isolated peritoneal metastasis of colorectal origin who received CRS and HIPEC in addition to systemic chemotherapy as compared to chemotherapy alone [4]. This study was heavily criticized already at the time of publication, as meanwhile systemic treatment options had evolved considerably. Indeed, survival rates for patients with stage IV disease treated with modern combination chemotherapy now exceed survival of the experimental arm in the Dutch trial [5]. However, the randomized data were confirmed by several large prospective studies showing superior survival figures for patients with isolated peritoneal metastasis of colorectal origin treated with CRS and HIPEC [2, 6, 7]. Thirteen years after the Dutch trial, in 2016, CRS and HIPEC was recommended for the first time in the ESMO guidelines for selected patients with peritoneal metastasis of colorectal origin [8]. Presented at the ASCO meeting 2018 [9], results from the French PRODIGE 7 randomized controlled trial are now challenging this recommendation again. The PRODIGE 7 trial is a French multicenter RCT, where 267 patients with peritoneal metastases (PCI < 25) were randomized to receive either CRS and HIPEC (oxaliplatin) or CRS alone in conjunction with systemic chemotherapy. No significant difference was found between the groups in terms of overall and disease-free survival, but 60 day major morbidity was higher in the HIPEC group. During the same meeting, results of the French PROPHYLOCHIP trial were presented, showing peritoneal metastasis in 52% of CT-negative patients and underlining the rationale for a second look strategy in these patients. However, prophylactic HIPEC added no benefit in terms of peritoneal relapse and overall survival at 3 years compared to surveillance alone. Thus, books are not closed for HIPEC for colorectal peritoneal metastasis and current recommendations might need to be revised.

Ironically, the image in ovarian cancer is like a negative of the picture obtained in colorectal cancer. In ovarian cancer, despite strong evidence showing superior outcomes of intraperitoneal chemotherapy in addition to systemic chemotherapy in three randomized trials [10], HIPEC failed to reach large acceptance among gynecological surgeons and oncologists. At the end of 2017, a

Dutch multicenter RCT documented increased overall and disease-free survival in ovarian cancer patients receiving CRS + HIPEC as compared to CRS alone [11], providing unequalled evidence in surgical therapy of ovarian cancer. Critics of this study were not long in coming and it is unclear at this point of time when this evidence level-I data will be included in therapy guidelines.

Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) is blowing fresh wind into this hot research landscape. First used in human in November 2011 [12], PIPAC is not even 7 years old and several RCTs have already been initiated. PIPAC technology was first developed and tested by a single team, including Phase-I [13] and Phase-II trials, and then carefully spread out to a handful of academic teams. Technology access was subject to participation to certification courses, so that current international practice is very homogenous in terms of indications, technique and treatment protocols [14]. The body of evidence is growing rapidly and the current results encourage further evaluation [15].

What was shown already?

- PIPAC can be safely implemented with minimal learning curve
- Repetitive PIPAC treatment is feasible and safe
- PIPAC has no negative impact on quality of life and symptoms
- Short-term oncological outcomes are favorable

What needs to be further investigated

- Oncological efficacy including long-term outcomes
- Long-term toxicity
- Confirmation of current indications, evaluation of extended indications
- Transition from empirical to evidence-based therapy protocols: choice of intraperitoneal drugs and drug combinations, dose-escalation protocols, duration, pressure, nebulizer technology; combined vs. sequential systemic treatment, etc.

As of June 10, at least 15 prospective studies on PIPAC were registered in public databases (NCT and Eudra-CT), including an international registry [16]. The protocols of three of these studies plus two new studies are presented in this issue of *Pleura and Peritoneum*.

Two protocols were elaborated by the group from Odense PIPAC center (OPC). PIPAC-OPC2 [17] is a prospective single center phase II study on treatment response in peritoneal cancer of different primaries. Primary outcome is histological response (assessed by PRGS) after three PIPAC treatments and estimated sample size is 137 patients. The same group launched a Phase-II protocol (PIPAC-OPC3) assessing PIPAC as adjuvant treatment in high-risk colon cancer patients after adjuvant systemic treatment [18]. Primary endpoint is 3 year peritoneal disease-free survival as assessed by CT scan. Of note, this study protocol is very similar to the French multicenter study PROPHYLOCHIP described above. It remains to be seen whether PIPAC can top HIPEC due to its pharmacokinetic advantages (distribution, tissue penetration, repeated administration).

Two study protocols evaluate a potential beneficial effect of adding PIPAC with cisplatin and doxorubicin to systemic chemotherapy. PIPAC EstoK 01 is a French multicenter randomized phase II study in gastric cancer patients who are no candidates for CRS and HIPEC (PCI > 8) [19]. Ninety-four patients shall be equally randomized to receive standard palliative combination chemotherapy alone (control) or in combination with 3 PIPAC procedures. Progression-free survival is the primary endpoint. A similar, German study protocol evaluates 3 × PIPAC in combination with FOLFOX vs. FOLFOX alone in patients with peritoneal seeding from upper GI tumors [20]. This international multicenter RCT aims at randomizing 206 patients. Primary endpoint is progression-free survival. Of note, both study protocols foresee the conservative empirical drug combination of cisplatin (7.5 mg/m^2) in combination with doxorubicin (1.5 mg/m^2) and not the new regimen defined by the dose-escalation study in ovarian cancer patients [2].

Finally, a fifth study protocol presented by the Gent group is evaluating a nanomolecule administered intraperitoneally as PIPAC. This is an international Phase I-II trial examining the effect of Albumin-stabilized paclitaxel nanoparticles (Abraxane^{TM}) in patients with peritoneal metastasis of various origins [21]. A Bayesian approach is applied in order to define the dose limiting toxicity as primary endpoint.

The only true wisdom is in knowing you know nothing, wrote Socrates 2500 years ago. Yes indeed, little is known about oncological efficacy of PIPAC at this point of time. However, it appears that lessons were learnt from the HIPEC experience and that PIPAC follows the "IDEAL framework of surgical innovation" [22–24].

Controlled implementation of PIPAC, a potentially toxic treatment, is warranted by certification courses and mentoring programs. Detailed description of technique, safety protocols, standardized perioperative pathways and checklists are freely accessible online [25]. Due to highly standardized therapy protocols [14], serious scientific evaluation of PIPAC has been started as reflected by the study protocols in this issue. In addition, the *real world experience* outside study protocols is captured by the international PIPAC registry. It remains to be awaited whether the PIPAC community is able to maintain this high standard of controlled implementation and standardization of treatment protocols with the rapid spread of this technology.

Yes, PIPAC is on the fast lane but speed limits need to be respected!

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