Editorial

Martin Hübner

In search of evidence – PIPAC on the fast lane

https://doi.org/10.1515/pp-2018-0119

Keywords: pressurized intraperitoneal aerosol chemotherapy, peritoneal cancer, evidence, efficacy.

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/m²) in combination with doxorubicin (1.5 mg/m²) 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 intra-peritoneally as PIPAC. This is an international Phase I-II trial examining the effect of Albumin-stabilized paclitaxel nanoparticles (Abraxane™) 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!

Author contributions: The author has accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

References

1. Horton R. Surgical research or comic opera: questions, but few answers. Lancet 1996;347:984–5.
2. Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol 2004;22:3284–92.
3. Sugarbaker PH, Clarke L. The approval process for hyperthermic intraoperative intraperitoneal chemotherapy. Eur J Surg Oncol 2006;32:637–43.
4. Verwaal VJ, Van Ruth S, De Bree E, Van Sloothen GW, Van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003;21:3737–43.
5. Petrelli F, Borgonovo K, Cabiddu M, Ghilardi M, Lonati V, Massero F, et al. FOLFIRI-bevacizumab as first-line chemotherapy in 3500 patients with advanced colorectal cancer: a pooled analysis of 29 published trials. Clin Colorectal Cancer 2013;12:145–51.
6. Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol 2010;28:63–8.
7. Franko J, Shi Q, Meyers JP, Maughan TS, Adams RA, Seymour MT, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. Lancet Oncol 2016;17:1709–19.
8. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Adorka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386–422.
9. http://abstracts.asco.org/214/AbstractView_214_222851.html Consulted 11 Jun 2018.
10. Jaaback K, Johnson N, Lawrie TA. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. Cochrane Database Syst Rev 2016;CD005340. doi:10.1002/14651858.CD005340.pub4
11. Van Driel WJ, Koole SN, Sonke GS. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med 2018;378:1363–4.
12. Solass W, Kerb R, Murdter T, Giger-Pabst U, Strumberg D, Tempfer C, et al. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. Ann Surg Oncol 2014;21:553–9.
13. Tempfer CB, Giger-Pabst U, Seebacher V, Petersen M, Dogan A, Reznicek GA. A phase I, single-arm, open-label, dose escalation study of intraperitoneal cisplatin and doxorubicin in patients with recurrent ovarian cancer and peritoneal carcinomatosis. Gynecol Oncol 2018 May 6. Epub ahead of print. DOI:10.1016/j.ygyno.2018.05.001
14. Nowacki M, Alyami M, Villeneuve L, Mercier F, Hubner M, Willaert W, et al. Multicenter comprehensive methodological and technical analysis of 832 pressurized intraperitoneal aerosol chemotherapy (PIPAC) interventions performed in 349 patients for peritoneal carcinomatosis treatment: an international survey study. Eur J Surg Oncol 2018;44:991–6.
15. Grass F, Vuagniaux A, Teixeira-Farinha H, Lehmann K, Demartines N, Hubner M. Systematic review of pressurized intraperitoneal aerosol chemotherapy for the treatment of advanced peritoneal carcinomatosis. Br J Surg 2017;104:669–78.
16. https://www.clinicaltrials.gov/ct2/results?cond=PIPAC&term=&cntry=&state=&city=&dist=. Consulted 11 Jun 2018.
17. Graversen M, Deltesfen S, Asmussen J, Mahdi B, Frstrup C, Pfeiffer P, et al. Treatment of peritoneal carcinomatosis with Pressurized IntraPeritoneal Aerosol Chemotherapy – PIPAC-OPC2. Pleura and Peritoneum 2018;3. DOI: https://doi.org/10.1515/pp-2018-0108.
18. Graversen M, Deltesfen S, Asmussen J, Mahdi B, Frstrup C, Pfeiffer P, et al. Adjuvant Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) in resected high-risk colon cancer patients – study protocol for the PIPAC-OPC3 trial. A prospective, controlled phase 2 study. Pleura and Peritoneum 2018;3. DOI: https://doi.org/10.1515/pp-2018-0107.
19. Eveno C, Jouvin I, Pocard M, Estok PIPAC. 01: pressurized Intraperitoneal Aerosol Chemotherapy with cisplatin and doxorubicin (PIPAC C/D) in gastric peritoneal metastasis: a randomized
and multicenter phase II study. Pleura and Peritoneum 2018;3. DOI: https://doi.org/10.1515/pp-2018-0116.

20. Goetze TO, Al-Batran SE, Pabst U, Reymond M, Tempfer C, Bechstein WO, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) in combination with standard of care chemotherapy in primarily untreated chemo naïve upper GI adenocarcinomas with peritoneal seeding – A phase II/III trial of the AIO/CAOGI/ACO. Pleura and Peritoneum 2018;3. DOI: https://doi.org/10.1515/pp-2018-0113.

21. Ceelen W, Van De Sande L, Graversen M, Hübner M, Pocard M, Reymond M, et al. Intraperitoneal aerosolization of albumin-stabilized paclitaxel nanoparticles (Abraxane™) for peritoneal carcinomatosis from upper GI, breast, or ovarian cancer – a phase I first-in-human study. Pleura and Peritoneum 2018;3. DOI: https://doi.org/10.1515/pp-2018-0112.

22. Ergina PL, Barkun JS, McCulloch P, Cook JA, Altman DG. IDEAL Group. IDEAL framework for surgical innovation 2: observational studies in the exploration and assessment stages. BMJ 2013.346:f3011.

23. McCulloch P, Cook JA, Altman DG, Heneghan C, Diener MK. IDEAL Group. IDEAL framework for surgical innovation 1: the idea and development stages. BMJ 2013.346:f3012.

24. Cook JA, McCulloch P, Blazeby JM, Beard DJ, Marinac-Dabic D, Sedrakyan A. IDEAL Group. IDEAL framework for surgical innovation 3: randomised controlled trials in the assessment stage and evaluations in the long term study stage. BMJ 2013.346:f2820.

25. Hübner M, Grass F, Teixeira-Farinha H, Pache B, Mathevet P, Demartines N. Pressurized IntraPeritoneal Aerosol Chemotherapy – Practical aspects. Eur J Surg Oncol 2017;43:1102–9.

Martin Hübner, Department of Visceral Surgery, Lausanne University Hospital CHUV, Bugnon 46, Lausanne 1011, Switzerland, E-mail: martin.hubner@chuv.ch