Cytoreductive surgery and intraperitoneal hyperthermic perfusion

Many neoplastic diseases progress to peritoneal surface malignancies (PSM), with a poor prognosis. Cytoreductive surgery and intraperitoneal hyperthermic perfusion have drastically changed the natural history of PSM.

HIGHLIGHTS

- Before the advent of cytoreductive surgery and intraperitoneal hyperthermic perfusion, peritoneal surface malignancy was considered terminal and only palliative treatment given.
- The procedure is complex, expensive and time consuming.
- More centres are needed to meet demand, and clear guidelines must be established.

Peritoneal surface malignancy (PSM) is a clinical entity with an unfavourable prognosis; it characterises the progression of neoplastic diseases from the abdominal and/or pelvic organs, and can also be the terminal stage of extraabdominal tumours. Examples of diseases that spread mainly within the peritoneal cavity are appendiceal tumours, ovarian cancer, colorectal cancer, abdominal sarcomatosis, gastric cancer and peritoneal mesothelioma.

Locoregional therapy is defined as the combination of cytoreductive surgery (CRS) and intraperitoneal hyperthermic perfusion (IPHP). PSM remains confined to the peritoneal cavity for most of its natural history – this pattern of spread indicates the potential usefulness of selectively increasing drug concentration in the tumour-bearing area by direct intraperitoneal chemotherapy instillation.

Cytoreductive surgery

Each procedure of the peritonectomy technique for CRS has a definite resection that requires an orderly sequence of surgical manoeuvres to create optimal cytoreduction. One or more of the following steps can be performed depending on the extension of primary surgical staging or disease spread at the time of laparotomy, in order to achieve optimal residual status:

- Greater omentectomy, right parietal peritonectomy and right colon resection;
- Left upper quadrant peritonectomy, splenectomy and left parietal peritonectomy;
- Right upper quadrant peritonectomy and Glissonian’s capsule resection;
- Lesser omentectomy, cholecystectomy, stripping of omental bursa and antrectomy;
- Pelvic peritonectomy with sigmoid colon resection with or without hysterectomy and bilateral salpingo-oophorectomy.
In the closed technique the skin of the abdominal wall is temporary closed with a running suture and Tenckhoff catheters connected to the circuit in order to initiate IPHP. In the open modality, also known as Coliseum technique, the abdomen is covered with a plastic sheet and drug vapour is evacuated to protect the operating room personnel.

The catheters are connected to the extracorporeal circuit and the preheated polysaline perfusate containing the drug combination is instilled in the peritoneal cavity using the heart–lung pump at a mean flow of 600-800 ml/min for 60/90 minutes.

State of the art: treatment indications and results

Indications for the use of CRS and IPHP include:
- Resectable peritoneal carcinomatosis (PC) from ovarian cancer after first-line chemotherapy (under phase III investigation);
- Peritoneal mesothelioma;
- Resectable PC from colorectal cancer;
- Mucinous tumour from the appendix with Pseudomyxoma peritonei;
- Carcinoma of the appendix with resectable PC;
- Gastric cancer with resectable PC.

Colorectal carcinoma In 2004 in Europe, colorectal cancer was the second most common form of cancer (381,000 cases) and second most common cause of death due to cancer (203,700 deaths). At initial diagnosis of colon cancer the peritoneal surface is involved in 10-15% of patients. Peritoneal surfaces are the second most common site for cancer recurrence after so-called curative.
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31. Mohamed F et al.
34. Bozzetti F et al.
24. Glehen O et al.
28. Verwaal VJ et al.
25. Deraco M et al.

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colorectal cancer resections, occurring in as many as 50% of patients.

A recent retrospective multicentre study reported on 506 patients with colorectal cancer treated with CRS and IPHP at 28 institutions. The overall median survival was 19.2 months. Verwaal et al conducted a prospective randomised study to confirm the findings from uncontrolled studies that CRS and IPHP is superior to standard treatment in 105 patients with PC from colorectal cancer.27 The median survival was 12.6 months in the standard therapy arm and 22.3 months in the CRS and IPHP therapy arm (log-rank test, P = 0.032).

**Gastric cancer** In 2004 in Europe, gastric cancer was the fifth most common form of cancer (171,000 cases) and third most common cause of death due to cancer (137,000 deaths). Yonemura et al [ref?] reported on 107 patients with peritoneal dissemination from gastric cancer treated with surgery (conventional or peritonectomy) and IPHP. The median survival for all patients was 11.5 months, with a five-year survival rate of 6.7%. The five-year survival rate after complete cytoreduction by peritonectomy with CHPP was 27%.

**Ovarian cancer** Ovarian cancer with an incidence of 44,000 cases a year in 2004 in Europe, remains the most lethal of all gynaecological malignancies, being responsible for about 50% of all deaths for female genital tract cancer.25 According to several phase II studies, the treatment of PC from ovarian cancer with CRS and IPHP has provided five-year overall survival rates ranging from 15% to 63% (Piso et al, Ryu et, Deraco et al)[refs?]

In order to confirm these apparently encouraging results, SITILO (Italian Society of Integrated Locoregional Therapy) is conducting a prospective multicentre randomised study to test the effectiveness of secondary CRS associated with IPHP in patients with epithelial ovarian cancer as second-line therapy.

**Appendiceal mucinous tumours and Pseudomyxoma peritonei (PMP)** Sugarbaker (2001) [ref?] reported 86% survival on 224 patient with PMP syndrome due to a mucinous appendiceal tumour. We reported (2004) on 33 patients with PMP treated with CRS and IPHP at the NCI of Milan (Figure 1).28 Five-year overall and progression-free survivals rates were 97% and 43%, respectively. Furthermore, in 2003 we published a large multicentre series of 70 patients with PMP who were enrolled onto a phase II SITILO clinical trial. Five-year overall survival, progression-free survival and locoregional progression-free survival were 91%, 54% and 69%, respectively.

**Peritoneal mesothelioma** Sebbag et al [ref?] reported on 33 patients with peritoneal mesothelioma treated by CRS with peritonectomy procedures and perioperative intraperitoneal chemotherapy (cisplatin, doxorubicin). Median survival was 31.0 months; overall projected survival at three years was 56%. In 2003 we published results obtained from 61 patients with PM enrolled onto a phase 2 SITILO multicentre clinical trial. Five-year overall and five-year progression-free survivals were 54% and 37%, respectively.

**Conclusion**

Locoregional treatment of PSM is attracting increased interest from the scientific community. The mean duration of the procedure according to the experience of NCI of Milan is nine hours; the average duration of hospitalisation is 23 days and the mean cost is €30,000. Instituting a programme in PSM requires not only highly specialised human resources but also complex technological facilities.

There are at least 60 active centres in Europe that have already set up PSM programmes. However, each centre is able to perform no more than 50-60 procedures per year due to its complexity. Considering the constant increase in the near future of the prevalence of diseases treatable by the procedure, more centres should be activated. The establishment of clear policy and scientific guidelines is mandatory in order to perform the CRS and IPHP safely, minimising treatment-related morbidity and mortality and maximising results in terms of survival and quality of life.

Five-year forecast

- More randomised data for each disease are necessary to confirm the efficacy of this complex approach
- Studies on biological markers with prognostic value should also be conducted to improve the indications of the procedure
- A multicentre cooperative consensus is required to standardise the technique and define scientific guidelines