Treatment Options for Peritoneal Tumor Recurrence

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Multimodal therapy of peritoneal carcinomatosis, including maximal cytoreduction, hyperthermic intraperitoneal chemotherapy, and systemic therapy, leads to a significant increase of disease-free survival and overall survival in strictly selected patients. This treatment is offered in curative intent. However, in reality, for the majority of patients, peritoneal carcinomatosis is a recurrent and persistent problem.

- Most tumor recurrences are intraabdominal. Even after initial complete cytoreduction and intraperitoneal chemotherapy, in most cases tumors recur solely in the peritoneal cavity.

In approximately 80% of patients with peritoneal carcinomatosis of colorectal carcinoma, for 24–44% of patients with pseudomyxoma peritonei, and 40% of patients with mesothelioma, tumor recurrence is confined to the peritoneum after previous cytoreductive surgery and intraperitoneal chemotherapy [10].

- Depending on the patient population, 4–16% of all previously multimodally treated patients are considered to be candidates for a successful iterative cytoreduction [4].

For strictly selected patients, there is a chance of long-term tumor control and improved overall survival.

- Through this aggressive approach 1-, 3-, and 5-year survival rates of 92%, 60%, and 34% were possible for different tumor entities in a mixed patient sample.

So far, no selection criteria for repeated cytoreductive surgery with intraperitoneal chemotherapy have been defined. Therefore, patient selection is extrapolated from the established selection criteria for cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) (Table 40.1). Early diagnosis of the recurrence is crucial for improved survival. Isolated peritoneal recurrence after CRS and HIPEC usually occurs in the mid-term postoperative course. Patients who are deemed eligible for iterative cytoreduction should receive a follow-up at intervals of 3–6 months within the initial 5 years [10]. Tumor recurrence usually affects the visceral peritoneum. Therefore, tumor distribution primarily determines resectability. A structured postoperative follow-up ensures the recognition of patients with localized recurrence

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Table 40.1 Selection criteria

Pro	Contra
ECOG performance status 0–1	Extraabdominal metastases
CC0 resection in previous CRS	Small bowel PCI >2
Favorable tumor biology	Small bowel syndrome
Long disease-free interval	Malnutrition
Chance of a CC0 cytoreduction	Serious comorbidity
Localized tumor	Retroperitoneal tumor
	Diffuse/multilocular peritoneal metastases

and low tumor burden. Early re-intervention in locally limited tumor manifestations minimizes the extent of subsequent visceral peritonectomy procedures. Thus the extent of iterative cytoreduction is usually less extensive than previous resections.

Despite the very complex surgery, the rate of grade III/IV complications remains within an acceptable range. The incidence of postoperative complications correlates with the peritoneal carcinomatosis index and ranges between 2.3% and 40% [6, 7, 9].

In several studies, HIPEC was a positive prognostic parameter [4, 7]. Especially with recurrences in the short-term follow-up, a change of intraperitoneally applied chemotherapeutic drugs seems advisable. However, clear recommendations cannot be made as long as data is insufficient.

5-year survival rates of 53% and 75% were achieved for pseudomyxoma peritonei [3–5, 11]. Due to its biology, pseudomyxoma peritonei is suitable for iterative cytoreductive surgery. In pseudomyxoma peritonei, extra-abdominal metastases are rare. Thus a local procedure seems particularly promising. Especially low-grade tumors show predominantly expansive and only minimally invasive growth. The recurrent tumor distributes at anatomic predilection sites, such as sites for peritoneal fluid resorption, and mostly spares the small intestine. Therefore, repeated surgery is often possible while avoiding a short bowel syndrome. Prognostically favorable parameters after repeated CRS and HIPEC are complete cytoreduction (CCR-0 resection) and a significantly lower peritoneal carcinomatosis index (<50%) compared to initial surgery. In addition, the abdominal regions treated during initial cytoreduction must remain free of disease or show only minimal tumor progression [5].

For colorectal carcinoma, study results vary. In an older retrospective study, with a median survival of 23 months, 1- and 3-year survival rates were 90% and 0% [4]. In another case series, 1- and 2-year survival rates were 74% and 50% [8]. During a median follow-up period of only 10 months, 78% of patients were diagnosed with a—usually intraabdominal—tumor recurrence after a second cytoreduction and intraperitoneal chemotherapy. The median disease-free time was only 4.5 months. In contrast to these disappointing results, the evaluation of current data for 189 patients with isolated peritoneal recurrence and iterative CRS and HIPEC yielded a median survival of 46.2 months and 1-, 3-, and 5-year survival rates of 96.5%, 66.3% and 41.6% [1]. All studies published are retrospective case series with a correspondingly low level of evidence. However, recent results from the largest published case study suggest that long-term tumor control can be achieved in peritoneal metastasized colorectal cancer by repeated CRS and HIPEC. The indication for a second cytoreduction and repeated intraperitoneal chemotherapy should be based on a strict patient selection and consideration of possible alternative treatments. Decisions regarding surgical treatment must be primarily based on the characteristic of intraabdominal recurrence. The completeness of cytoreduction (CC score) is the major determinant of survival. Patients with incomplete cytoreduction do not benefit from the multimodal treatment. As complete cytoreduction is only possible in localized disease, patients with diffuse peritoneal metastases do not benefit from repeated CRS and HIPEC [2].

Peritoneal mesothelioma is a very rare tumor. Therefore, data on repeated CRS and HIPEC in peritoneal recurrence is poor. So far there are only retrospective studies with a very small number of cases. In the largest case study available, 44 patients with peritoneal tumor recurrence

achieved a median survival of 54 months with CRS and HIPEC [7]. The 3- and 5-year survival rates were 61% and 46%. The survival rates for patients with optimal cytoreduction tumor recurrence were nearly identical to the survival rates for patients with a CCR-0 resection following the initial procedure (3-year survival 60%, 5-year survival 52%). Similar survival rates were reported in a study by Chua et al. (median survival 57 months, 3- and 5-year survival rates 80% and 27%) [4]. Positive prognostic criteria were young patient age, an interval between first and second CRS and HIPEC of more than 18 months, minor tumor growth on the small intestine, and the performance of hyperthermic intraperitoneal chemotherapy.

40.1 Conclusion

For patients with isolated peritoneal recurrence after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, there is currently no standardized approach. The decision for a second or further CRS and HIPEC must be made on an individual basis, taking into account the tumor biology and the expected postoperative quality of life. Due to the complexity of the procedure, both patient selection and surgery should be performed at a high-volume center. The most important prognostic criterion is the ability to achieve complete cytoreduction. Therefore a CCR-0 situation after the first peritonectomy is usually considered mandatory for a successful second intervention. However, a CCR-1 or CCR-2 situation after the initial procedure is not an absolute contraindication for further cytoreduction if there is a chance of achieving complete cytoreduction in the subsequent, more extensive procedure. The extent of resection must be determined while taking into consideration the expected postoperative quality of life. Despite the methodological weaknesses of retrospective studies, the good survival rates in selected patients and the as-yet unsatisfactory systemic treatment options justify a second or repeated CRS and HIPEC for pseudomyxoma peritonei, peritoneal mesothelioma, and colorectal carcinoma. In conclusion, an iterative CRS and HIPEC is another treatment option in addition to palliative systemic therapy for strictly selected patients.

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