Surgical Oncology 28 (2019) 159–166

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

HIPEC and CRS in peritoneal metastatic gastric cancer - who really benefits?

Thomas Hotopp

Medizinisches Versorgungszentrum des Deutschen Roten Kreuzes, An der Wipper 2, 06567, Bad Frankenhausen, Germany

ARTICLE INFO

Keywords:
Gastric cancer
HIPEC
Score
Temperature

ABSTRACT

Background: Gastric cancer with the presence of peritoneal metastases (pmgc) is associated with a very poor prognosis. Despite the wide utilization and promising results of the multimodal treatment regimens including cytoreductive surgery (CRS) and a subsequent hyperthermic intraperitoneal chemotherapy (HIPEC), it is still not fully understood which patient group is suitable for this treatment.

Methods: Twenty-six patients (median age 53 years, range 39–71) were scheduled for three cycles of neoadjuvant systemic chemotherapy using bi-weekly FLOT-protocol followed by CRS + HIPEC. After this treatment 3 additional cycles of FLOT were given. During HIPEC Oxaliplatin was applied in a dosage of 200 mg/m^2 and Docetaxel in a dosage of 80 mg/m^2.

Results: All patients underwent the standardized multimodal treatment including FLOT, CRS and HIPEC. This treatment resulted in an overall survival (OS) of 17 months in comparison to 6 months as the outcome of the classic treatments. Regression analysis demonstrated a Peritoneal Cancer Index (PCI) ≥ 12 as a negative factor for survival. Furthermore, we could see a worse prognosis by a higher temperature (> 41,4 °C) of the chemotherapy used for the HIPEC.

In consideration of the gender, the histomorphology and the Laurén-classification, we could develop a precise score to define the patient group which will benefit from this multimodal treatment with a prognosis improvement of 24 months.

Conclusion: Neoadjuvant chemotherapy using the FLOT-protocol followed by CRS + HIPEC seems to be associated with prolonged OS in patients with peritoneal carcinomatosis from gastric cancer. This treatment needs a critical evaluation for patients with a PCI ≥12.

Furthermore, the accurate selection of patients suffering of PMGC by using the developed score can improve the OS of up to 24 months for a suitable group and it can avoid the extensive treatment for unsuitable patients.

1. Background

Gastric carcinoma is one of the most common malignancies worldwide and is currently the fourth most common solid tumor. Although the incidence of new cases in Germany has fallen in the last 30 years, the relative 5-year survival rates of around 30% across all stages remain unfavorable [1].

The prognosis for patients with a metastatic situation is also unsatisfactory; at the stage of peritoneal metastasis, the average survival is less than 6 months [2].

There are numerous international studies and publications describing multimodal treatment concepts that appear to improve the prognosis for the corresponding patients [3–5].

The role of surgical therapy in peritoneal metastatic gastric carcinoma (pmgc) is still unclear. However, there is evidence that certain patients with limited peritoneal metastasis may benefit from maximal surgical therapy. The problem so far is the identification of suitable patients.

Within the scope of the present retrospective monocentric observational study, patients with a peritoneal metastatic gastric cancer were recorded over a longer period, who were subjected to a multimodal treatment concept. The aim of the work is to record pre- and intraoperative indicators to obtain clues as to which patients benefit from this regimen and which group should be treated for palliative therapy.

2. Methods

2.1. Patient population

At our clinic, various medical data was analyzed retrospectively of patients who were treated with the combination of perioperative chemotherapy and CRS with HIPEC between August 2008 and April 2013.

During this period, 26 patients were subjected to the regime, 14 of

E-mail address: thomas.hotopp@kliniken-drk.de.

https://doi.org/10.1016/j.suronc.2019.01.005
Received 4 November 2018; Received in revised form 17 December 2018; Accepted 6 January 2019

them were female, 12 males.

Inclusion criteria were confirmed peritoneal metastasis of gastric carcinoma and a Karnofsky index > 70%.

Patients who have undergone pre-treatment with surgical resection or systemic chemotherapy have not been studied. Similarly, a distant metastasis in extra abdominal organ systems was an exclusion criterion.

Depending on the patient's place of residence, the re-evaluation was carried out either by a restaging carried out in our clinic or by telephonic questioning of the general practitioner or the patient with the request for the transmission of all laboratory chemical and imaging findings.

2.2. Multimodal treatment concept

2.2.1. Primary staging

In all patients, the carcinoma was detected by esophagogastroduodenoscopy. At least 8–10 biopsies of the suspicious structures were taken. Peritoneal metastasis was confirmed by abdominal CT or PET-CT or laparoscopic surgical exploration. This primary diagnosis was partly done in our clinic, but also patients from other locations in Germany presented themselves for treatment in our department, where these examinations were carried out abroad. All these external pretherapeutic findings were available to us.

2.2.2. Treatment strategy

All patients were submitted to the FLOT scheme. They received preoperatively each 3 cycles of the known scheme. After completion of neoadjuvant therapy, patients were referred for definitive surgery. To ensure a homogeneity of the procedure, all interventions were carried out exclusively by a surgeon who has enough experience with this technique and has published his own results [6]. The aim of the operation was to achieve macroscopic tumor clearance. With this intention, the total gastrectomy was performed in all cases with reconstruction by a switched-off jejunal loop according to Roux-Y in combination with a D2 lymph node dissection. Peritoneal seeding was categorized by Sugarbaker PCI. Peritonectomy was performed according to the method also described by PH Sugarbaker [7]. In several cases, mutiviszerale resection was required as part of the targeted R0 resection.

The final macroscopic tumor clearance was recorded with the Completeness of Cytoreduction Score (CCS).

It was also investigated whether and to what extent ascites was present.

The postoperative complication rate was recorded using the Clavien-Dindo classification.

For the intraperitoneal administration of cytostatic, we used the open Colosseum technique as standard.

For 45 min, 4000 ml of the rinse solution was perfused at a desired temperature of 41.5 °C at a flow rate of 1500 ml/min.

The drugs used were regularly 80 mg/m^2 taxotere and 200 mg/m^2 oxaliplatin. After completion of the surgical performance and an average convalescence of 3 weeks, it was attempted to complete the systemic chemotherapy with another 3 cycles according to the FLOT scheme.

2.2.3. Re-evaluation and statistical evaluation

Depending on the patient's place of residence, the re-evaluation was carried out either by a restaging carried out in our clinic or by a telephone survey of the general practitioner or the patient with the request for the transmission of all current laboratory and imaging findings.

Median survival, defined as the time of first diagnosis up to the date of death of the patient or the time of the last patient contact, was recorded with the log rank test and presented in Kaplan-Meier curves.

The status was "alive" or "deceased". The cause of death could not be clearly defined in all cases, so the distinction between tumor progression, recurrence, secondary diseases or other causes is not possible.

Furthermore, the 30-day mortality was recorded as postoperative mortality.

The age and gender distribution were described descriptively, as well as the pre-, intra- and postoperative findings.

The influence of different histopathological, intraoperative and postoperative findings on overall survival was also statistically represented using the Kaplan-Meier estimator.

For relevant questions concerning the relationships of individual factors, a correlation analysis according to Spearman was performed.

In assessing the relationship between nominal and metric characteristics, logistic regression analysis was used.

The significance level was set at $p < 0.05$ for all surveys.

3. Results

The following criteria were considered in the evaluation:

- gender and age of patients
- existence of ascites
- histomorphology
- TNM-classification
- Peritoneal Cancer Index (PCI)
- extent of surgery
- maximum temperature of HIPEC.

An overview of the examined criteria and their influence on overall survival is shown in Table 1.

All 26 patients could be included in the evaluation. At the time of the first diagnosis, the median age was 50 years (range 39–71).

The incidence of peritoneal carcinomatosis was documented by Sugarbaker's PC index. The median PCI was 10 (range 5–24).

Since the presence or amount of the ascites should be included in

Table 1
Influence of different criteria on overall survival.

criteria	dependent variable		p-value
gender	male (n = 12)	female (n = 14)	0.024
age	< 50 years (n = 13)	≥50 years (n = 13)	0.33
existence of ascites	-(n = 18)	+ (n = 8)	0.359
T	< 4 (n = 11)	= 4 (n = 15)	0.543
N	-(n = 6)	+ (n = 20)	0.786
V	-(n = 14)	+ (n = 12)	0.025
histomorphology	adenocarcinoma (n = 17)	signet ring carcinoma (n = 9)	0.052
Lauren type	intestinal (n = 8)	diffuse or mixed type (n = 18)	0.001
PCI	< 12 (n = 14)	≥12 (n = 12)	0.069
resection of other organs (extent of surgery)	< 6 (n = 21)	≥6 (n = 5)	0.001
maximum temperature of the HIPEC	< 41,4 °C (n = 15)	≥41,4 °C (n = 11)	0.014

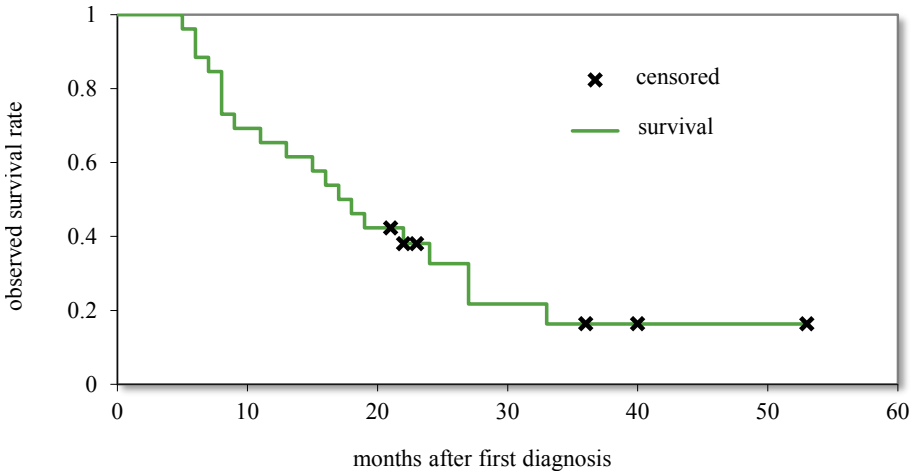

Fig. 1. Survival probability of the whole patient collective.

the evaluation, the intraoperatively found volumes were also recorded.

The intention of gastrectomy with D2-lymphadenectomy was met in all documented cases. Likewise, the peritonectomy was performed.

In only 2 patients' resection was limited to gastrectomy and peritonectomy, 2 operations required resection of 7 other organs. The median shows 3 additional resection measures per procedure.

A complete resection (CC 0 and CC 1) could be achieved in all cases.

The postoperative complications were recorded if they occurred during the inpatient stay in our clinic. Two complications could be managed conservatively, in 5 patients a relaparotomy was required during inpatient treatment. A total of 93 applied intestinal sutures showed 2 anastomotic leakages and 1 duodenal stump insufficiency.

The preparations showed in most of the tubular adeno- and signet ring carcinomas.

The Laurén subtypes were represented approximately in equal proportions.

The Her2-neu status was recorded in 24 patients; it was negative in all cases.

About the T-category as well as the grading, the majority showed T4a - as well as a predominant proportion of poorly differentiated carcinomas.

In 76.9% of the cases there was a positive lymph node involvement. On average, 28 lymph nodes were resected per procedure (range 12–60). This showed a median positive lymph node involvement of 4 (range 0–34).

Postoperatively, after a convalescence of 3 weeks on average, chemotherapy could be continued according to the FLOT schedule. Neither postoperative complications nor other causes delayed the initiation of therapy. This was completed in 77%. 6 out of 26 patients died under the current postoperative treatment.

3.1. Statistical long-term recording

All patients were followed up. Time of the last survey was the 1st July 2014.

The 30-day mortality was at 0%. The earliest death occurred at day 42; the patient died due to tumor progress. The longest observation period of the surviving patients was 53 months. By 01st July 2014, a total of 20 patients had died. In the case of currently 6 survivors, the survival rate up to the last patient contact is 23%.

Median survival (defined as the time of first diagnosis to death) was calculated to be 17 months (Fig. 1).

3.2. Long-term assessment for the preoperative findings

The preoperative findings were recorded and related to overall survival. We examined the grading, the histological Laurén typing and the histomorphology of the primum.

The patient's gender and age were included in the evaluation at the time of the first diagnosis. For relevant influences, the probability of survival according to Kaplan-Meier is shown. There were predominantly G3 carcinomas, a G1 situation was found in any findings. An influence of grading on survival cannot be assessed. A total of 9 signet ring and 17 adenocarcinomas showed a trend towards a longer median survival for patients with adeno versus signet ring carcinoma ($p = 0.052$, Fig. 2).

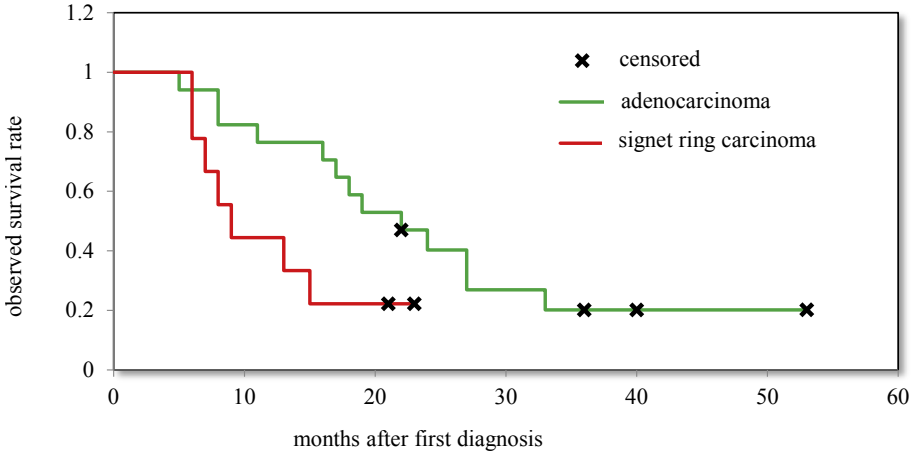

Fig. 2. Influence of histomorphology on survival ($p = 0.052$).

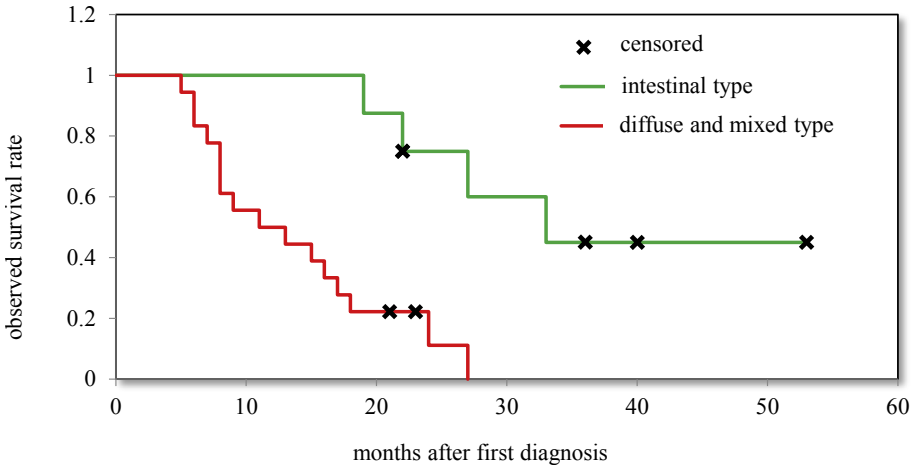

Fig. 3. Influence of the Laurén classification on survival (p = 0.001).

A dependence of the overall survival on the age of the patients at the time of the diagnosis could not be statistically proven. With approximately the same distribution of Laurén types (Table 1), there is a statistically significant survival advantage for patients with intestinal type according to Laurén versus diffuse or mixed type (p = 0.001, Fig. 3).

Based on the available data, an influence of the patient's gender on the prognosis can be shown. Female patients had a significantly shorter overall survival than male patients (p = 0.024, Fig. 4).

3.3. Development of a reproducible score based on preoperative prognostic factors

Based on the above-mentioned, prognostically significant preoperative parameters, a scoring system was developed in accordance with the aim of this work, which should enable a preoperative prognosis estimation. Significance was shown only for the patient's sex, the histomorphology of the tumor and its Laurén typing. These parameters were nominally scaled and assigned to empirically collected values. The result is a flowchart with the attached form (Fig. 5).

The score assigned to the individual parameters was determined purely empirically and does not define the significance of a characteristic expression. From a score of 7 and above, a significantly poorer prognosis for median survival is shown (Fig. 6).

Thus, in the patient's group with a score of 6 and lower, there was a median survival of 24 months, while the group with the worse prognosis had only a total survival of 8 months.

Compared with the statistically known survival probability of 6 months [2] at pmgc, patients with a score > 6 show only a minimal survival advantage, which should put the benefit of multimodal treatment into perspective when making an individual therapy decision.

3.4. Long-term assessment after the postoperative findings

After resection, a definitive pTNM classification could be performed. This was set according to the T, N, L, V and R category in relation to the medial survival and evaluated with the survival analysis. Neither for the T-category nor for lymph node involvement could a statistically significant impact on overall survival be demonstrated. A lymphatic vessel invasion was seen in 24 patients, but only 2 cases could not be detected. A statistical evaluable evaluation was therefore not possible. In 46% of the cases a venous vascular invasion was detected histologically. This significantly influences the observed survival (p = 0.025).

3.5. Long-term assessment after intraoperative findings

Ascites were only found in 8 patients. In the survival analysis, these patients were compared with the unremarkable group, as well as a possible influence of the ascites on the prognosis and the surgical outcome was investigated. In addition, the importance of a complete surgical resection regarding the long-term prognosis was investigated. Here we compared the number of resected regions after Sugarbaker with the probability of survival. The number of additional resected organs showed a statistically significant relationship with overall survival. Thus, after 6 further intraabdominal resections per patient

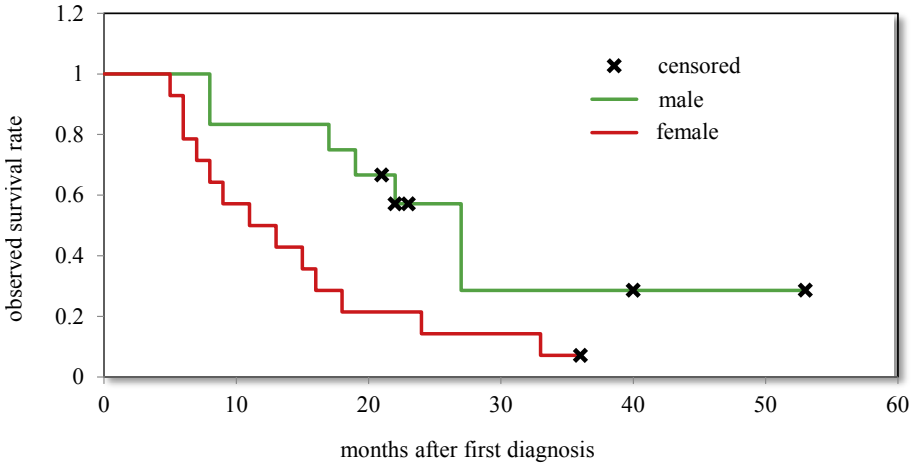

Fig. 4. Influence of sex on survival (p = 0.024).

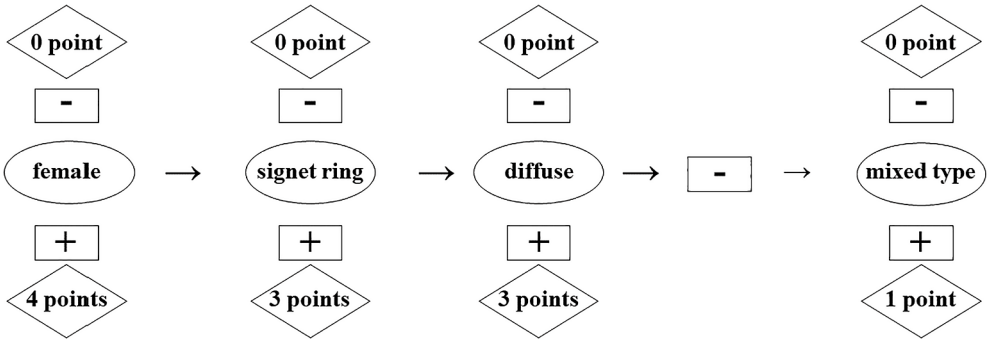

Fig. 5. Flowchart for determining the preoperative score.

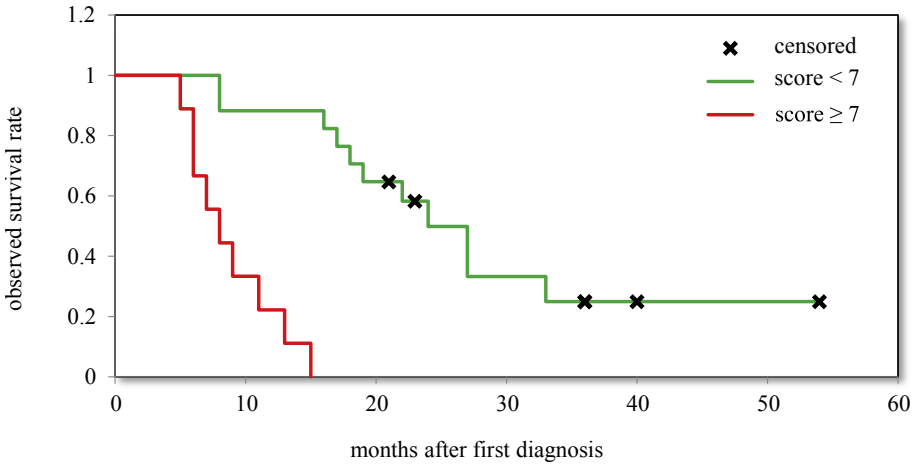

Fig. 6. Survival probability depending on preoperative score (p = 0.001).

(n = 5) the median survival decreases significantly (p = 0,001). Intraoperatively found PCI was related to median survival. Here, there is a trend towards a reduced overall survival rate for patients with PCI ≥12 (p = 0.069).

Furthermore, a statistically detectable influence of the temperature of the intraperitoneal cytostatic at the time of application (so-called inflow temperature) on the median survival.

The median temperature was 41.3 °C, with a minimum of 40.8 °C and a maximum of 42.1 °C. According to an empirical analysis, survival rates are significantly lower from a temperature of 41.4 °C (p = 0.014, Fig. 7).

3.6. Long-term recording of the postoperative course

During the evaluation, the postoperative course was also examined. The complication rate and the rate of required surgical reinterventions were considered. Neither the number nor severity of the complications had a statistically tangible impact on overall survival. Likewise, any reintervention that may be required did not influence the probability of survival.

3.7. Correlations of the individual factors

To clarify the question of whether and to what extent individual

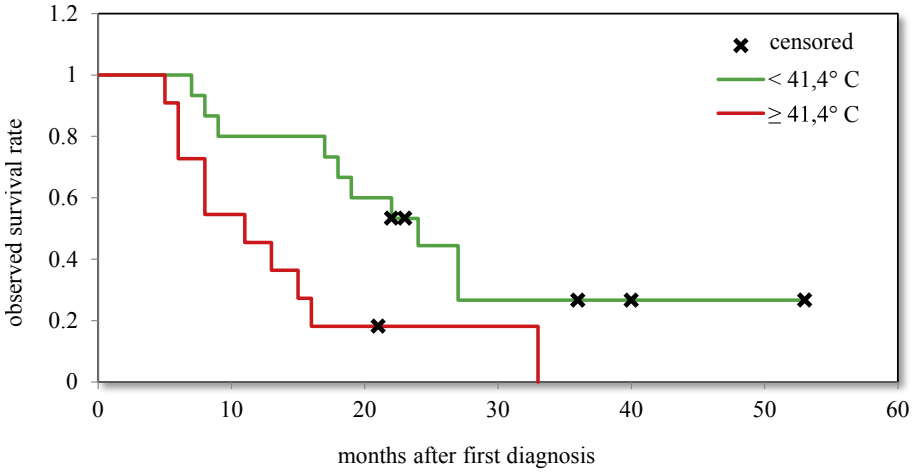

Fig. 7. Influence of cytostatic temperature on survival (p = 0.014).

factors influenced each other, we performed the correlation analysis according to Spearman.

There is a clear linear relationship between the PCI and the extent of peritonectomy and a moderate correlation between the PCI and the number of resected organs.

Another statistically detectable moderate relationship was found between the PCI and the maximum temperature of the applied cytostatic.

The number of postoperative complications correlates with the PCI and extent of peritonectomy moderately.

There was no tangible correlation between the complication rate and the number of resected organs.

There is a moderate negative relationship between the age of the patients and the presence of ascites. The older the patient was, the less frequently ascites was detected.

4. Discussion

4.1. Methods

Considering the exclusion criteria mentioned above, only a relatively small number of cases was considered in the examined period, which can therefore only be assessed statistically to a limited extent. However, at least trends can be described. Another limitation of the investigation arises from the retrospective nature of the work. It must be emphasized, however, that the entire therapy was standardized. So, we used the same perioperative chemotherapy protocol and a constant HIPEC procedure in all patients. All interventions were performed by only one surgeon. The histopathological examinations of the resected organs after definitive surgery were performed in the same institute.

4.2. Choice of intraperitoneal chemotherapeutic agents

We used the drugs oxaliplatin and docetaxel as part of HIPEC, which were already part of the perioperative FLOT regimen in all patients. The scheme was chosen because the study results with a response rate of 57.7% [8] are now well established.

Docetaxel is approved for the treatment of gastric carcinoma in Germany. The recommended dosage for systemic therapy is 75 mg/m^2. Muller et al. demonstrated in 2012 that taxanes show a similar side-effect profile in hyperthermic intraperitoneal administration as with systemic administration [9]. Our 80 mg/m^2 intraperitoneal dose is based on the idea of achieving the best possible effect with tolerable side effects. This view is purely empirical and currently not explicable and certainly worthy of discussion.

Oxaliplatin is currently used in the FLO (T) regimen for the treatment of metastatic gastric carcinoma with similar efficacy to cisplatin but with better tolerability.

Depending on the user, intraperitoneal dosing ranges from 300 mg/m2 to 460 mg/m^2 [10,11]. However, only accurate data on the use of oxaliplatin as part of HIPEC in the treatment of peritoneal metastatic colorectal carcinoma have been published so far.

A published recommended intraperitoneal dose of the drug for the treatment of pmgc is not available at the time of writing this paper.

Thus, our dosage of 200 mg/m^2 was also empirically determined to keep the side effect spectrum at a low level.

Non-evidence-based levels of intraperitoneally administered drugs are a common problem in HIPEC therapy worldwide. Further research into the optimal dosages of intraperitoneally administered chemotherapeutic agents in HIPEC, not just pmgc, is urgently needed.

4.3. The PCI and the median survival

At the present time there is no clear recommendation which PCI the benefit of a combination therapy for the treatment of pmgc is still useful and prognostically favorable for the patient. An independent review of the current data by the “Berufsverband Deutscher Chirurgen” (Professional Association of German Surgeons) concludes that the combination of complete cytoreduction and HIPEC should limit survival in advanced gastric carcinoma with peritoneal carcinoma to patients with PCI < 10 [12].Rudloff et al. set the limit for a PCI of ≤15 [13], while Glehen et al. questioned the usefulness of the method from a PCI of 12 [14].The data of the present work seems to lead to the conclusion that in fact a PCI greater than 11 does not significantly improve the prognosis of patients despite a multimodal therapy concept.

4.4. Prognostic factor of the ascites

The treatment results demonstrated here cannot demonstrate a clear association between the presence of ascites and the disease prognosis. This contradicts some studies in which a correlation is assumed. For example, Benizri et al. demonstrate that the mere existence of ascites negatively impacts the rate of completion of cytoreductive surgery and thus the prognosis [15]. This assumption has currently been made by Randle et al. confirmed [16].

However, the evaluation of the present work seems to require a more differentiated analysis. In our data, the correlation between ascites and the CCS could not be confirmed. The relatively small number of patients could be responsible for this result.

But considering the relationship between ascites and age it is noticeable that there is a statistically relevant inverse reciprocal relationship. Apparently, a higher age goes hand in hand with lower ascites or the chance of not developing ascites (Table 2). A direct causal relationship cannot be derived from this, there are no published data on this.

Perhaps a progressive degeneration of the peritoneum may be discussed, with a decrease in the ability to secrete fluid intra-abdominally. Further physiological studies regarding the age-dependent development of the peritoneum also seem to make sense here. If the above assumption is confirmed, Ascites cannot be directly influenced by the prognosis of peritoneal metastasis in gastric carcinoma, unless the patient's age is included in risk assessments and treatment decisions.

4.5. Influence of resection extent

Our retrospective studies show that overall survival significantly worsened after the resection of more than 5 organs ($p = 0.001$). It can be assumed that the extent of resection correlates with the tumor load quantified by the PCI. Present data seem to confirm this assumption.

Since the complication rate does not statistically increase with surgical radicality, the extent of peritoneal metastasis per se may be causally responsible for the worsening prognosis.

4.6. Maximum temperature of HIPEC and median survival

In the above results, increasing the inflow temperature of the intraperitoneally applied chemotherapeutic agents seems to worsen the prognosis of the patients. Currently known data and studies in this respect are sometimes quite contradictory in their statement.

The positive effect of HIPEC in the treatment of pmgc has been demonstrated in numerous studies [17,18] and the biological relationships have been investigated several times [19–21]. There are

Table 2
Correlation of the age of the patient at the time of initial diagnosis with the detection of ascites.

correlation between age of the patient and the presence of ascites	
r_s (Spearman's correlation)	– 0.428
p	0.029
n	26

also studies on temperature-dependent pharmacokinetics with evidence of positive effects at higher temperatures of the drugs doxorubicin at 43 °C [22] and mitomycin C at 42 °C [23].

Verhulst published a study that demonstrated a negative effect of increasing the temperature of oxaliplatin in HIPEC in terms of postoperative survival [10].

This coincides with our results. So far, this effect could not be clarified clearly.

It may be that an increase in the temperature of the cytostatic agents present in the peritoneal cavity can influence the pharmacokinetics of the cytostatic drugs.

There is currently at least one study investigating the stability of paclitaxel under the influence of temperature. Here, the maximum stability of the drug was 41.5 °C [24]. At the present time there are no studies investigating the stability of oxaliplatin and docetaxel under the influence of temperature. Whether parallel properties exist here, therefore remains only speculation.

In summary, it cannot be clarified in the present work why the increased inflow temperature negatively influences the prognosis. Due to the small number of cases, it is certainly possible to discuss a statistical inaccuracy, although influences of factors not examined here are equally possible for these results.

4.7. Preoperative score

An important intention of the work was to find out whether it is possible to identify factors that significantly influence the prognosis of the course of the disease already pretherapeutically.

By examining a statistically relevant influence of findings at diagnosis, appropriate evidence for gender, histomorphology and the Laurén classification of the tumors can be found.

Empirical determination of a score shows a highly significant influence of these factors on overall survival. Thus, a tool appears to be available to us that excludes patients with a score of 7 or more from a multimodal therapy, since the prognosis is not significantly improved despite this treatment. If appropriate, alternative methods, such as e.g. a sole chemotherapy or a best supportive care in the context of palliative-medical complex treatment should be offered.

4.8. Postoperative score

An attempt was made to develop a risk assessment in the sense of a further scoring system after gaining insights from intraoperative and postoperative findings. This is, of course, statistically limited use after exclusion of patients who must leave the evaluation after application of the preoperative score. Only 17 patients score < 7 remained for such a rating.

Prognostic factors were included in the considerations that had a significant influence on the course of the disease. This concerns the possible venous invasion, the ovarian metastasis, the maximum temperature of the perfused cytostatic and the PCI. Here, considering the above-mentioned restrictions, neither the individual finding nor the sum of the factors could be shown to have a positive or negative influence. The course of the disease thus does not appear to be influenced by further clinical, intraoperative and histological findings for this patient clientele.

This emphasizes the importance of applying a pretherapeutic risk assessment through the above-mentioned scoring system. No other factors seem to influence the course of pmgc as well as the sex and histomorphology of the primum.

5. Summary

Even today, peritoneally metastatic gastric carcinoma represents a prognostically unfavorable clinical picture. In recent years, however, various therapeutic regimens have been introduced which at least partially improved the prognosis of patients. These include multimodal treatment concepts that combine systemic perioperative chemotherapy and surgical cytoreduction with HIPEC. These procedures, which in some cases take up considerable resources, must be viewed critically economically and ethically. However, the available data indicate that at least selected patients can benefit from intensified multimodal therapy.

It could be demonstrated in this work that the combination of a neoadjuvant chemotherapy according to the FLOT scheme with a cytoreductive surgery and the HIPEC and subsequent re-systemic therapy after FLOT can increase the median survival to at least 17 months.

The differentiated statistical evaluation could identify prognostic factors that positively or negatively affect overall survival.

Thus, a better prognosis in patients of male sex and in adenocarcinomas of the intestinal type.

No influence on the prognosis could be demonstrated for the ascites, the age of the patients, the extent of resection and the complication rate.

A prognostically unfavorable parameter for median survival seems to be PCI ≥12, however, only a trend is indicated in this retrospective analysis.

A significant negative influence on the median survival seems to be the temperature of the HIPEC used chemotherapeutic agents > 41.4 °C. This correlation has not yet been finally clarified and encourages further investigations.

Based on these results, a pretherapeutic score was developed that includes parameters such as the sex and histomorphology of the primary tumor and may contribute to the profound selection of patients who benefit from multimodal therapy.

Disclaimer

The views expressed in the submitted article are my own and not an official position of the institution.

References

[1] Zentrum für Krebsregisterdaten, Krebs in deutschland 2007/2008 [online], Institut Robert Koch, Hrsg. Gesundheitsberichterstattung des Bundes, 2012.
[2] J.D. Spiliotis, E.A. Halkia, E. Efstathiou, Peritoneal carcinomatosis 2011; it's about time for chemosurgery, J. B.U.ON 16 (3) (2011) 400–408.
[3] G. Glockzin, P. Piso, Current status and future directions in gastric cancer with peritoneal dissemination, Surg. Oncol. Clin. 21 (4) (2012) 625–633.
[4] X. Liu, H. Cai, W. Sheng, Y. Wang, Long-term results and prognostic factors of gastric cancer patients with microscopic peritoneal carcinomatosis, PLoS One 7 (5) (2012) e37284.
[5] M. Ströhlein, S. Gläser, N. Cerasani, M. Heiss, Peritoneal metastasiertes Magenkarzinom: Ist die zytoreduktive Chirurgie und HIPEC nach induktiver Chemotherapie eine sinnvolle Therapieoption? [Abstract], Deutsche Gesellschaft für Chirurgie, Hrsg. 130. Kongress der Deutschen Gesellschaft für Chirurgie, Düsseldorf, German Medical Science GMS Publishing House, 2013.
[6] H. Müller, R. Hilger, Curative and palliative aspects of regional chemotherapy in combination with surgery, Support. Care Canc. 11 (1) (2003) 1–10.
[7] P.H. Sugarbaker, Management of peritoneal-surface malignancy: the surgeon's role, Langenbeck's Arch. Surg. 384 (6) (1999) 576–587.
[8] S.E. Al-Batran, J.T. Hartmann, R. Hofheinz, N. Homann, V. Rethwisch, S. Probst, Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie, Ann. Oncol. 19 (11) (2008) 1882–1887.
[9] M. Muller, M. Chérel, P.F. Dupré, S. Gouard, M. Collet, J.M. Classe, The cytotoxic effect of combined hyperthermia and taxane chemotherapy on ovarian cancer cells: results of an in vitro study, Eur. Surg. Res. 48 (2) (2012) 55–63.
[10] J. Verhulst, Hyperthermic intraperitoneal chemoperfusion with high dose oxaliplatin: influence of perfusion temperature on postoperative outcome and survival [Online], F1000 Research - Open for Science, 2013 Hrsg. Unter http://f1000research.com/articles/2-179/vl.
[11] G. Glockzin, M. Gerken, S.A. Lang, M. Klinkhammer-Schalke, P. Piso, H.J. Schlitt, Oxaliplatin-based versus irinotecan-based hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal metastasis from appendiceal and colorectal cancer: a retrospective analysis, BMC Canc. 14 (2014) 807.
[12] R. Hoerbelt, A. Griessemer, J. Gehron, W. Padberg, HIPEC-Verfahren bei der Behandlung der Peritonealkarzinose - standortbestimmung, aktuelle Datenlage [Online], BDC-online, Hrsg, 2014.
[13] U. Rudloff, R.C. Langan, J.E. Mullinax, J.D. Beane, S.M. Steinberg, T. Beresnev, Impact of maximal cytoreductive surgery plus regional heated intraperitoneal

chemotherapy (HIPEC) on outcome of patients with peritoneal carcinomatosis of gastric origin: results of the GYMSSA trial, J. Surg. Oncol. 110 (3) (2014) 275–284.
[14] O. Glehen, F.N. Gilly, C. Arvieux, E. Cotte, F. Boutitie, B. Mansvelt, Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy, Ann. Surg. Oncol. 17 (9) (2010) 2370–2377.
[15] E.I. Benizri, J.M. Bereder, A. Rahili, J.L. Bernard, D. Benchimol, Ascites and malnutrition are predictive factors for incomplete cytoreductive surgery for peritoneal carcinomatosis from gastric cancer, Am. J. Surg. 205 (6) (2013) 668–673.
[16] R.W. Randle, K.R. Swett, D.S. Swords, P. Shen, J.H. Stewart, E.A. Levine, K.I. Votanopoulos, Efficacy of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in the management of malignant ascites, Ann. Surg. Oncol. 21 (5) (2014) 1474–1479.
[17] Z.G. Zhu, R. Tang, M. Yan, J. Chen, Q.M. Yang, C. Li, Efficacy and safety of intraoperative peritoneal hyperthermic chemotherapy for advanced gastric cancer patients with serosal invasion. A long-term follow-up study, Dig. Surg. 23 (1–2) (2006) 102–193.
[18] G. Wei, G.E. Fang, J.W. Bi, X.J. Shen, M.M. Nie, X.C. Xue, J.D. Hua, Efficacy of intraoperative hypotonic peritoneal chemo-hyperthermia combined with early postoperative intraperitoneal chemotherapy on gastric cancer, Chin. J. Canc. 24 (4) (2005) 478–482.
[19] L.E. Gerweck, Hyperthermia in cancer therapy: the biological basis and unresolved questions, Cancer Res. 45 (8) (1985) 3408–3414.
[20] J.R. Oleson, S.K. Calderwood, C.T. Coughlin, M.W. Dewhirst, L.E. Gerweck, F.A. Gibbs, D.S. Kapp, Biological and clinical aspects of hyperthermia in cancer therapy, Am. J. Clin. Oncol. 11 (3) (1988) 368–380.
[21] S. Lindquis, The heat-shock response, Annu. Rev. Biochem. 55 (1986) 1151–1191.
[22] P. Jacquet, A. Averbach, O.A. Stuart, D. Chang, P.H. Sugarbaker, Hyperthermic intraperitoneal doxorubicin: pharmacokinetics, metabolism, and tissue distribution in a rat model, Cancer Chemother. Pharmacol. 41 (2) (1998) 147–154.
[23] P.H. Sugarbaker, D. Chang, Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy, Ann. Surg. Oncol. 6 (8) (1999) 727–731.
[24] W. Bouquet, W. Ceelen, B. Fritzinger, P. Pattyn, M. Peeters, J.P. Remon, C. Vervaet, Paclitaxel/beta-cyclodextrin complexes for hyperthermic peritoneal perfusion - formulation and stability, Eur. J. Pharm. Biopharm. 66 (3) (2007) 391–397.