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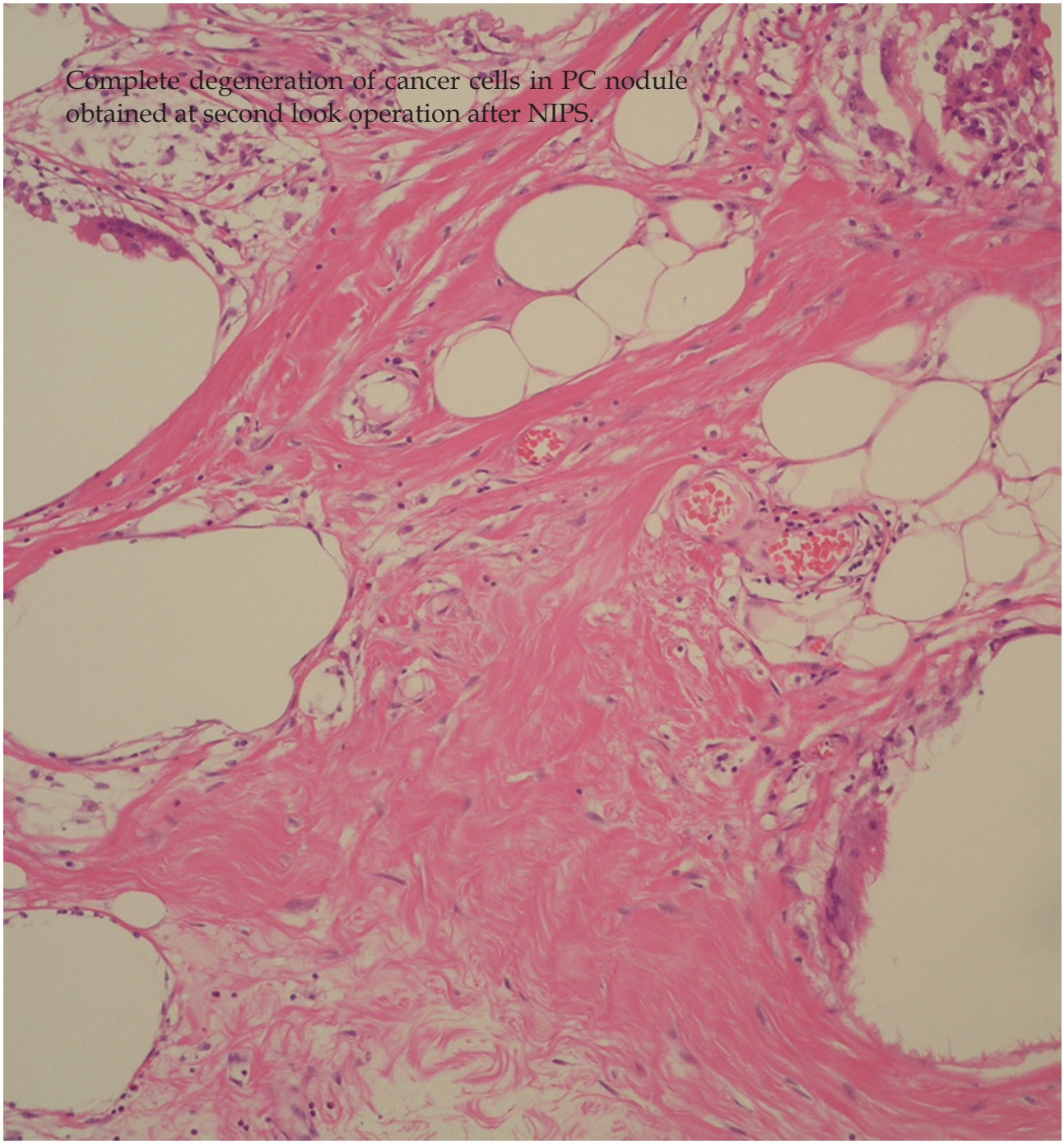

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Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: 0086-10-8538-1892
Fax: 0086-10-8538-1893
E-mail: baishideng@wjgnet.com
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EDITING
Editorial Board of *World Journal of Gastrointestinal Oncology,*
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
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Telephone: +0086-10-8538-1891
Fax: +0086-10-8538-1893
E-mail: wjgo@wjgnet.com
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Beijing Baishideng BioMed Scientific Co., Ltd.,
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No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: 0086-10-8538-1892
Fax: 0086-10-8538-1893
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Room 903, Building D, Ocean International Center,
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EDITORIAL

Early-onset gastric cancer: Learning lessons from the young

Anya N Milne, G Johan A Offerhaus

Anya N Milne, Department of Pathology, University Medical Centre Utrecht, Postbus 85500, 3508 GA, Utrecht, The Netherlands
G Johan A Offerhaus, Department of Pathology, Academic Medical Centre, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands
Author contributions: Milne AN designed the study and wrote the paper; Offerhaus GJA provided significant intellectual content and critically revised the manuscript.
Correspondence to: Anya N Milne, PhD, Department of Pathology, University Medical Centre Utrecht, Postbus 85500, 3508GA, Utrecht, The Netherlands. a.n.a.milne@umcutrecht.nl
Telephone: +31-30-2507663 Fax: +31-30-2544990
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Peer reviewer: László Herszényi, MD, PhD, Associate Professor, 2nd Department of Medicine, Semmelweis University, H-1088 Budapest, Szentkiralyi Str 46, Hungary

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Abstract

There is by no means a clear-cut pattern of mutations contributing to gastric cancers, and gastric cancer research can be hampered by the diversity of factors that can induce gastric cancer, such as *Helicobacter pylori* infection, diet, ageing and other environmental factors. Tumours are unquestionably riddled with genetic changes yet we are faced with an unsolvable puzzle with respect to a temporal relationship. It is postulated that inherited genetic factors may be more important in early-onset gastric cancer (EOGC) than in gastric cancers found in older patients as they have less exposure to environmental carcinogens. EOGC, therefore, could provide a key to unravelling the genetic changes in gastric carcinogenesis. Gastric cancers occurring in young patients provide an ideal background on which to try and uncover the initiating stages of gastric carcinogenesis. This review summarizes the literature regarding EOGC and also presents evidence that these cancers have a unique molecular-genetic phenotype, distinct from conventional gastric cancer.

Key words: Gastric cancer; Early-onset gastric cancer; *Helicobacter pylori*

INTRODUCTION

Gastric cancer is the fourth most common malignancy in the world and ranks second in terms of cancer-related death[1]. It is thought that gastric cancer results from a combination of environmental factors and the accumulation of generalized and specific genetic alterations, and consequently affects mainly older patients often after a long period of atrophic gastritis. The most common cause of gastritis is infection by *Helicobacter pylori* (*H. pylori*), which is the single most common cause of gastric cancer[2,3] and has been classified by the World Health organization (WHO) as a class I carcinogen since 1994[4]. The risk of infection varies with age, geographical location and ethnicity, but overall 15%-20% of infected patients develop gastric or duodenal ulcer disease and less than 1% will develop gastric adenocarcinoma[4]. Environmental and other risk factors for gastric cancer are summarised in Table 1 and have been recently reviewed by Milne *et al*[5,6].

A pattern of gastritis has also been shown to correlate strongly with the risk of gastric adenocarcinoma. The presence of antral-predominant gastritis, the most common form, confers a higher risk of developing peptic ulcers; whereas corpus predominant gastritis and multifocal atrophic gastritis lead to a higher risk of developing gastric ulcers and subsequent gastric cancer[7,8]. The response to *H. pylori* infection and the subsequent pattern of gastritis depends on the genotype of the patient and in particular a polymorphism in IL-1β, an inflammatory mediator triggered by *H. pylori* infection, is known to be of importance[9]. Multifocal atrophic gastritis is usually accompanied by intestinal metaplasia and leads to cancer *via*

dysplasia, and thus intestinal metaplasia is considered to be a dependable morphological marker for gastric cancer risk. Unlike intestinal gastric cancer, the diffuse type typically develops following chronic inflammation without passing through the intermediate steps of atrophic gastritis or intestinal metaplasia.

Several classification systems have been proposed, but the most commonly used are those of the WHO and of Laurén who describes two main histological types, diffuse and intestinal[10]. Intestinal adenocarcinoma predominates in high-risk areas whereas the diffuse adenocarcinoma is more common in low-risk areas[11]. Although classification varies between Japan and the West, attempts have been made recently to standardize systems[12]. Early gastric cancer is a term to describe carcinomas limited to the mucosa or to both the mucosa and submucosa, regardless of nodal status. The prevalence of this lesion is higher in countries such as Japan, where a screening programme is carried out.

There is by no means a clear-cut pattern of mutations in gastric cancers, with no known multi-step pathway, and genetic research can often be hampered by the diversity of changes that are induced by *H. pylori* infection, diet, ageing and other environmental factors. Tumours are unquestionably riddled with genetic changes, as summarized in Figure 1, yet we are faced with an unsolvable puzzle with respect to a temporal relationship. In order to solve this problem, one approach is to investigate tumours that are less influenced by these environmental factors. Gastric cancers occurring in young patients, known as early-onset gastric cancers (EOGC), provide an ideal background on which to try and uncover the initiating stages in gastric carcinogenesis. In addition, hereditary cancers can often illuminate discrete mutations that can initiate the pathway of gastric carcinogenesis.

Table 1 Environmental and other risk factors for conventional gastric cancer

Increased risk of gastric cancer	Decreased risk of gastric cancer
CHD1, TP53, BRCA2 germline mutation	Fruit and vegetables
Hereditary non-polyposis colorectal cancer	Ascorbic acid
Helicobacter pylori infection	Carotenoids
Ebstein barr virus infection	Folates
Cigarette smoking	Tocopherols
Smoked or cured meat and fish	Cereal fibres
Pickled vegetables	Numerous polymorphisms
Chilli peppers	(as mentioned under
Alcohol	increased risk)
Exposure to nitrosamines + inorganic dust	
Obesity	
Pharmacological gastric acid suppression	
IL-1β-31 polymorphism	
1195 COX-2 polymorphism	
Other polymorphisms: MTHFR, PSCA, XPA, XPC, ERCC2, GSTT1, SULT1A1, NAT2, EPHX1, Toll-like receptor 4	

EARLY ONSET GASTRIC CANCER

Gastric cancer is rare below the age of 30 thereafter it increases rapidly and steadily to reach the highest rates in the oldest age groups, both in males and females. The intestinal type rises faster with age than the diffuse type and is more frequent in males than in females. EOGC is defined as gastric cancer presenting at the age of 45 or younger. Approximately 10% of gastric cancer patients fall into the EOGC category[13], although rates vary between 2.7%[14] and 15%[15] depending on the population studied. Young patients more frequently develop diffuse lesions, which often arise on the background of histologically "normal" gastric mucosa. It is postulated that genetic factors may be more important in EOGC than in older patients as younger patients have less exposure to environmental carcinogens[5,16], thus these cancers could provide a key to unravelling the genetic changes in gastric carcinogenesis. *H. pylori* may still play a role in the development of gastric cancer in young patients[17-19], and there is, in fact, no difference in the distribution of gastric cancer predisposing *IL1β* polymorphisms between young and old patients[20]. However, the role of *H. pylori* is likely to involve a much smaller percentage of patients than in the older age group. Epstein-Barr virus (EBV), which is observed in 7%-20% of gastric cancers, has been implicated in gastric carcinogenesis and occurs slightly more frequently in diffuse-type gastric cancers[21-23]. However, the levels of EBV infection appear to be much lower (or absent) in EOGC[24].

The clinicopathological features of gastric carcinoma are said to differ between young and elderly patients[25] and it has been claimed that young patients have a poorer prognosis[26]. Others report that tumour staging and prognosis for young patients is similar to older patients and depends on whether the patients undergo a curative resection[13,15,27]. Young patients with gastric cancer in the United States are more likely to be black, Asian or Hispanic[28]. Relative to older patients, young patients have a female preponderance, a more frequent occurrence of diffuse cancer and less intestinal metaplasia[13,28,29]. This predominance of females is considered by some to be due to hormonal factors[30,31]. Cancers in young patients are more often multifocal than in older patients[32] as is also seen in HDGC[33].

Approximately 10% of young gastric cancer patients have a positive family history[13], some of which are accounted for by inherited gastric cancer predisposition syndromes. Although the underlying genetic events are not always known, it can involve *CDH1* germline mutations[34-36], encoding an aberrant form of E-cadherin, resulting in hereditary diffuse gastric cancer (HDGC), as recently reviewed by Carneiro *et al*[36]. In fact, some suggest that when looking at *hMLH1* and *CDH1* germline mutations, 2%-3% of EOCG cases in North Americans may be due to high-risk genetic mutations[37,38]. The 90% without a family history emphasizes that the occurrence of gastric cancer in young patients remains largely unexplained, and is probably caused by a predisposing genotype that has facilitated cancer development due various environmental triggers[6].

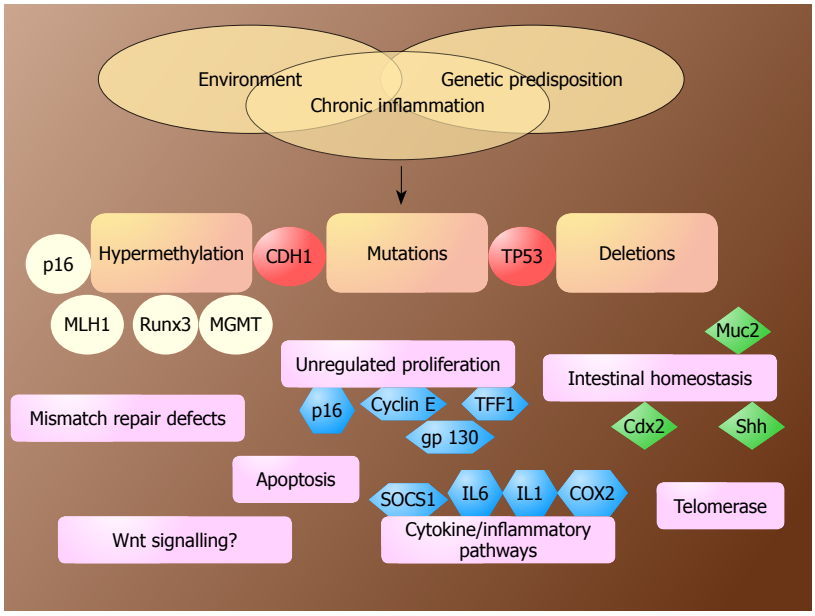

Figure 1 This figure summarizes the molecular genetic changes in conventional gastric cancer and emphasizes the lack of a multi-step pathway in gastric cancer, despite extensive research in the field. It highlights the need for a new approach to understanding gastric cancer, such as examining early-onset gastric cancers and hereditary gastric cancers, where we can learn from the young.

It has been discovered that EOGCs have a different clinicopathological profile than conventional gastric carcinomas. This suggests that they represent a separate entity within gastric carcinogenesis and indeed evidence at a molecular genetic level supports this. The majority of gastric adenocarcinomas, like many other solid tumours, show defects in the maintenance of genome stability, resulting in DNA copy number alteration that can be analysed by (microarray-based) comparative genomic hybridization (array CGH). Hierarchical cluster analysis of array CGH data on 46 gastric cancer patients (including 12 young patients) revealed clusters with genomic profiles that correlated significantly with age[39]. Gains at chromosomes 17q, 19q and 20q have been found in EOGC with comparative genomic hybridization[40] and LOH findings have also shown that losses are infrequent in EOGC[24].

The presence of microsatellite instability (MSI), which usually occurs at a frequency of 15%-20% in older gastric carcinomas, also varies dramatically between gastric cancer in young and old patients, with MSI consistently absent in EOGC[24,29,41,42]. These results have been found despite the analysis of distal tumours (where MSI is usually more common) and inclusion of mixed and intestinal type tumours (diffuse tumours generally have less MSI)[43]. However, it may be that geographical factors play a role[44]. A lack of MSI excludes the mutator phenotype as an important predisposing factor in the development of EOGC. This contrasts with the situation in colorectal cancer where 58% of patients without HNPCC aged under 35 years showed evidence of MSI[45]. EOGC also contrasts with colorectal cancer with respect to the tumor suppressor gene *APC*, which causes familial adenomatosis polyposis syndrome. The role of *APC* in EOGC is limited and nuclear expression of β-catenin has not been found to differ between EOGC and conventional gastric cancers[46,47].

Molecular expression profiles of EOGC and conventional gastric cancers have been found to differ and EOGC has a COX-2 Low, TFF-1 expressing phenotype[46]. In light of studies showing the reduced risk of gastric cancer in non-steroidal anti-inflammatory drug users[48,49], these results may have clinical implications, as they suggest that this reduced risk may apply only to gastric cancer in older patients, as COX-2 does not appear to play an important role in EOGC. It also implies that genetic changes typical for conventional tumors more readily induce COX-2 expression than those associated with EOGC. Interestingly, this COX-2 low phenotype cannot be explained by the increased presence of the *COX2* -765 G>C polymorphism in EOGC[50]. A higher incidence of aberrant E-cadherin expression in EOGC regardless of histological type[29] has also been reported, although a more recent report that compared EOGC with conventional cancers showed that aberrant expression of E-cadherin correlated significantly with the diffuse type[46].

Deregulation of the cell cycle is known to be a critical event in the onset of tumourigenesis, and thus the finding of low molecular weight isoforms of cyclin E in EOGC, which are reported to be constitutively active in breast cancer[51], are of great interest. The expression of these isoforms differs between EOGC and conventional cancers, being present in 35% of EOGCs, compared to in 8% of conventional gastric cancers and 4% of stump cancers[52]. In addition, these low molecular weight isoforms in EOGC diverge from the classical role of cyclin E as oncogenes and were found to be an independent positive prognostic indicator in EOGC[52] adding to reports where the role of cyclin E conflicted with previous dogma[53,54]. This complexity of molecular wiring in carcinogenesis has also been emphasized in recent literature, with the conclusion that cancer can no longer be viewed purely in terms of a network of oncogenes and tumour suppressor genes[55,56].

Further evidence that EOGCs display molecular characteristics different from conventional carcinomas comes from a study where amplification at 11p12-13 was found in gastric cancer using representational difference analysis and was confirmed by Southern blot analysis. It

Table 2 Clinico-pathological and molecular-genetic differences between early-onset and conventional gastric cancers

Conventional gastric cancer	Early-onset gastric cancer	Ref.
Equally common in male and females	More common in females	[13,28,30,31]
Intestinal type cancer more common	Diffuse type cancer more common	[13,28]
Usually unifocal	Often multifocal	[32,33]
Often preceded by intestinal metaplasia	No intestinal metaplasia	[13,28]
Microsatellite Instability in 15%-20%	Lack of MSI	[24,29,41-43]
Commonly find loss of heterozygosity	Infrequent loss of heterozygosity	[24]
COX2 overexpression in 66%	COX2 overexpression in 10%	[46]
Loss of TFF1 expression in 73%	Loss of TFF1 expression in 39%	[46]
Loss of RUNX3 gene	No loss of RUNX3	[58-61]
Widespread gains throughout genome	Gains at chromosomes 17q, 19q and 20q	[40]
Distinct gene clusters on hierarchical analysis	Distinct gene clusters on hierarchical analysis	[39]
Infrequent LMW isoforms of cyclin E	Frequent LMW isoforms of cyclin E	[52]
CD44v6 expression	CD44v6 more commonly expressed	[57]
Usually no family history	10% with a family history	[13]

was found that overexpression of the isoform CD44v6 correlated with this amplification in diffuse type cancer and that this overexpression occurred more commonly in EOGC regardless of histological type[57].

The gene *RUNX3* has been a subject of great debate in gastric cancer studies in recent years, following a study where loss of the gene was shown to be associated with stimulated proliferation and suppressed apoptosis of gastric epithelial cells[58]. Conflicting evidence has, however, also been present, as the expression of RUNX3 in the gastric mucosa of mice differed significantly between strains analysed[59]. Furthermore, the gastric hyperplasia observed in the *Runx3*$^{-/-}$ mice used in Li's study was not observed in the mouse strain studied by Levanon *et al*[60]. Recent literature regarding *RUNX3* has excluded it as having a tumour suppressor function in EOGC[61], although as some of the cell lines used in this study were from conventional gastric cancers, the implications may be more far-reaching and call the importance of *RUNX3* in all gastric cancers into question.

Classic genetics alone cannot explain sporadic EOGC and cancer development in patients with a weak family history. The concept of epigenetics offers a partial explanation and may have important clinical implications for these types of cancer. The best-known epigenetic marker is DNA methylation, which occurs in CpG sites (islands), has critical roles in the control of gene activity, and is influenced by the modifications in histone structure that are commonly disrupted in cancer cells. Gene promoter methylation, a phenomenon that increases with age and may account for the increase in cancer in older age groups, has also been found to occur in EOGC[47]. However, comparison with the conventional group has not yet been carried out.

As supported by the literature, summarised in Table 2, EOGCs differ from conventional gastric cancers, not only at a clinicopathological level, but also at a molecular genetic level. If this is indeed due to the fact that the environment plays a smaller role in triggering the carcinogenic pathway, the investigation of this group of cancers may reveal genetic changes that assist in the task of putting forward a multistep pathway for gastric cancer.

FUTURE PROSPECTIVES

Gastric carcinoma continues to be a cause of premature death, despite progress in detection and treatment and despite advances in our understanding of the molecular basis of cancer. The need to develop efficient and effective cancer-specific drugs is coupled with the importance of accurate prediction of disease outcome for various patient groups, some of whom, due to the biology of their disease, will do better than others and may warrant a different treatment protocol. However, the multi-step pathway of carcinogenesis that occurs in some epithelial cancers and that has allowed accurate clinical and pathologic characterization is not yet elucidated in gastric cancer. Gastric cancers often occur without any consistent mutational abnormality and with considerable variation in pathogenesis ranging from a stepwise progression of changes to tumours arising in the absence of a precursor lesion. As has been highlighted in this article, there is growing evidence to support the hypothesis that young patients develop carcinomas with a different molecular genetic profile from that of sporadic carcinomas occurring at a later age. Further study of hereditary gastric cancers and EOGC as unique subsets of gastric cancer may aid us in the search for a gastric cancer pathway.

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EDITORIAL

The issue of lymphadenectomy during laparoscopic gastrectomy for gastric carcinoma

Muhammed Ashraf Memon, Nick Butler, Breda Memon

Muhammed Ashraf Memon, Nick Butler, Breda Memon, Department of Surgery, Ipswich Hospital, Chelmsford Avenue, Ipswich, Queensland 4305, Australia
Muhammed Ashraf Memon, Department of Surgery, University of Queensland, Mayne Medical School, Herston Road, Herston, Queensland 4006, Australia; Faculty of Helath Sciences and Medicine, Bond University, Gold Coast, Queensland 4229, Australia; Faculty of Health Sciences, Bolton University, Deane Road, Bolton, Lancashire BL3 5AB, United Kingdom
Author contributions: All authors were involved in drafting the manuscript and revising it critically for important intellectual content. Furthermore, all authors have participated sufficiently in the work to take public responsibility for its content.
Correspondence to: Muhammed Ashraf Memon, FRCS, FRACS, Professor, Department of Surgery, Ipswich Hospital, Chelmsford Avenue, Ipswich, Queensland 4305, Australia. mmemon@yahoo.com
Telephone: +61-448614170 Fax: +61-7-38101592
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Abstract

Surgical resection remains the mainstay of treatment for gastric cancer. Laparoscopic assisted gastrectomy has failed to gain universal acceptance as an alternative to the open approach for a number of reasons, one of which includes the issue of oncological radicality in terms of lymph node dissection. Nodal status, which is one of the most crucial and independent predictors of patient survival, therefore has been examined both in single institutional trials and also in randomised controlled trials especially on early gastric cancer. The issue of oncological adequacy for laparoscopic lymph node harvesting for advanced gastric cancer remains a contentious issue because of the unique challenges it poses in terms of complexity, safety and time, and also the lack of randomised controlled trials in this area. It is thus imperative that good quality multicentre randomised controlled trials are designed to investigate the benefits of extended lymphadenectomy in the setting of laparoscopic surgery, especially for advanced gastric cancer and its impact on both short and long term survival.

Key words: Gastrectomy; Meta-analysis; Randomised controlled trials; Laparoscopic method; Comparative studies; Retrospective trials; Lympadenectomy; Patient's outcome

Peer reviewer: Gregory Kouraklis, Associate Professor, Medical School, University of Athens, 122 Vasilisis Sofias Avenue, Athens 11526, Greece

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Minimal access gastrointestinal surgery for gastric cancer; i.e. laparoscopic distal gastrectomy (LDG), has not achieved universal acceptance by the surgical fraternity although introduced 13 years ago. The reasons are both technical and oncological. Recently, however, there has been a tremendous amount of advancement in the development of laparoscopic instruments which, coupled with increasing experience in the performance of complex laparoscopic gastrointestinal procedures, have led to the expansion of minimal access surgery for both benign and malignant gastric procedures. The following editorial will discuss some of these contentious issues and progress made in this area.

Laparoscopic assisted gastrectomy (LAG) for the management of gastric malignancy is becoming increasingly popular. It was introduced 13 years ago by a group of Japanese surgeons[1]. Its wider acceptance, however, as an alternative to the open approach remains a contentious subject, especially because of the technical difficulties involved in achieving an adequate lymph node dissection,

an issue that is viewed differently by Eastern and Western surgeons. Various trials have estimated that there will be lymph node involvement in 3%-5% of gastric cancer cases limited to mucosa only, 11%-25% lymph node involvement if the cancer involves submucosa, 50% lymph node involvement in T2 cancer and 83% lymph node involvement in T3 cancer[2,3]. Nodal status, thus, is one of the most crucial and independent predictors of patient survival[4,5]. Therefore, the issue of oncology radicality for lymph node harvesting, especially for both early and advanced gastric cancer during LAG, remains hotly debated because of the unique challenge it poses in terms of complexity, safety and time. Many gastrointestinal surgeons, at least in the West, consider laparoscopic D2 lymph node dissection to be tedious, onerous, unnecessary and even unsafe. This assumption is based on a number of randomised controlled trials (level I evidence) comparing open D1 *vs* D2 lymphadenectomy for gastric cancer, which has shown no long term survival advantage and a higher perioperative complication rate and death in the D2 group[6,7]. Furthermore, the cochrane Review[8] has confirmed these findings. However, many groups, especially from the East, differ on this issue based on their large retrospective data showing significant benefits and modest morbidity from extended lymph node dissection. Some of the groups with extensive open D2 experience have since consolidated their experience with LAG and have now published randomised controlled trials (RCTs) comparing LDG and open distal gastrectomy (ODG)[9-12]. The RCTs have examined the issue of laparoscopic radicality of lymph node dissection mainly in early gastric cancer. To date, all the RCTs (level I evidence) have found lymph node retrieval during a laparoscopic procedure to be not only sufficient but meeting the global standard for adequate staging, emphasizing the oncological radicality of laparoscopic gastric procedures[13]. In fact, in none of the RCTs was there any significant statistical difference in lymph node retrieval for the two procedures. However, a recent meta-analysis[14], which pooled together the results of four RCTs, has come to a different conclusion altogether. The authors of this meta-analysis[14] have shown that there was a statistically significant reduction in lymph node harvesting for LDG compared to ODG, which may translate into an overall survival disadvantage for patients having LDG. As the long term results for the majority of these trials have not been published, this assumption is difficult to corroborate. However, the long term results are eagerly awaited.

The argument on the merits and risks of extended lymph node clearance for AGC during LAG is additionally controversial because of the absence of level I or II evidence. Hwang *et al*[15] reported their experience of LAG for AGC. They compared LAG (n = 45) with ODG (n = 83) performed between 2004 and 2007 in a non-randomized fashion. These authors found no difference in the mean number of nodes harvested in either group and felt that extended lymphadenectomy for AGC is possible and safe. Furthermore, the authors felt that there was good evidence that LAG was superior in improving the quality of life. However, the mean follow-up of the patients was around two years and therefore long term results in terms of disease free survival and mortality are not known. Similarly, Kawamura *et al*[16] in yet another non-randomized trial comparing LDG (n = 53) and ODG (n = 67) over a two year period examined the safety and accuracy of D2 dissection for AGC. They concluded that D2 dissection could be performed safely and accurately without undue complications provided the surgical team was skilled in minimally invasive surgical techniques. However, they conceded that no long term results for LDG for AGC are available and therefore the need for an RCT is important to address this issue.

Zhang *et al*[17] looked at 10 years of experience in their unit with 391 laparoscopic gastrectomies from 1998 to 2007. In 100 patients (25.6%), the number of lymph nodes retrieved was less then 15. This number is less than one would expect even for D1 lymphadenectomy suggesting that the extent of lymphadenectomy achieved by these authors in a quarter of their patients did not approach the global standard for accurate staging. The findings of this trial suggest that even in experienced hands and in large volume centres, extended lymphadenectomy poses a challenge.

Nodal status, whether in LDG or ODG, remains the most important independent predictor of gastric cancer patient survival. The RCTs comparing LDG versus ODG for early gastric cancer have shown that the extent of lymphadenectomy achieved by current laparoscopic procedures approaches the global standard for accurate staging. Performing extended resection laparoscopically as recommended in Japan remains a challenge and is a time consuming process as evident from the Zhang *et al*[17] study. Therefore, laparoscopic gastrectomy for AGC may only be justified under the setting of clinical trials in a high volume centre and in the hands of experienced laparoscopic gastric surgeons. Given the vast difference between Eastern and Western surgeons in surgical experience in gastric cancer surgery, and the difference in the prevalence of gastric cancer between the East and West and a higher rate of complications associated with a more aggressive resection, it is imperative that surgeons in the East take the lead in organising a good quality multicentre randomised controlled trial enrolling a large number of patients to address the issue of LDG versus ODG for the treatment of gastric cancer, with a main emphasis on extended lymph node resection and its impact on both short and long term survival.

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TOPIC HIGHLIGHT

Antonio Macrì, MD, Professor, *Series Editor*

Hyperthermic intraperitoneal chemotherapy: Rationale and technique

Santiago González-Moreno, Luis A González-Bayón, Gloria Ortega-Pérez

Santiago González-Moreno, Luis A González-Bayón, Gloria Ortega-Pérez, Peritoneal Surface Oncology Program, Department of Surgical Oncology, Centro Oncológico MD Anderson International España, 28033 Madrid, Spain
Author contributions: González-Moreno S, Ortega-Pérez G, and González-Bayón LA designed, discussed the paper contents and collected pertinent information; González-Moreno S wrote the paper.
Correspondence to: Santiago González-Moreno, MD, PhD, Peritoneal Surface Oncology Program, Department of Surgical Oncology, Centro Oncológico MD Anderson International España, Calle Arturo Soria 270, 28033 Madrid, Spain. sgonzalez@mdanderson.es
Telephone: +34-91-7878600 Fax: +34-91-7680681
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Abstract

The combination of complete cytoreductive surgery and perioperative intraperitoneal chemotherapy provides the only chance for long-term survival for selected patients diagnosed with a variety of peritoneal neoplasms, either primary or secondary to digestive or gynecologic malignancy. Hyperthermic intraperitoneal chemotherapy (HIPEC) delivered in the operating room once the cytoreductive surgical procedure is finalized, constitutes the most common form of administration of perioperative intraperitoneal chemotherapy. This may be complemented in some instances with early postoperative intraperitoneal chemotherapy (EPIC). HIPEC combines the pharmacokinetic advantage inherent to the intracavitary delivery of certain cytotoxic drugs, which results in regional dose intensification, with the direct cytotoxic effect of hyperthermia. Hyperthermia exhibits a selective cell-killing effect in malignant cells by itself, potentiates the cytotoxic effect of certain chemotherapy agents and enhances the tissue penetration of the administered drug. The chemotherapeutic agents employed in HIPEC need to have a cell cycle nonspecific mechanism of action and should ideally show a heat-synergistic cytotoxic effect. Delivery of HIPEC requires an apparatus that heats and circulates the chemotherapeutic solution so that a stable temperature is maintained in the peritoneal cavity during the procedure. An open abdomen (Coliseum) or closed abdomen technique may be used, with no significant differences in efficacy proven to date. Specific technical training and a solid knowledge of regional chemotherapy management are required. Concerns about safety of the procedure for operating room personnel are expected but are manageable if universal precautions and standard chemotherapy handling procedures are used. Different HIPEC drug regimens and dosages are currently in use. A tendency for concurrent intravenous chemotherapy administration (bidirectional chemotherapy, so-called "HIPEC plus") has been observed in recent years, with the aim to further enhance the cytotoxic potential of HIPEC. Future trials to ascertain the ideal HIPEC regimen in different diseases and to evaluate the efficacy of new drugs or drug combinations in this context are warranted.

Key words: Hyperthermia; Intracavitary chemotherapy; Peritoneal neoplasms; Peritoneal carcinomatosis; Cytoreductive surgery

Peer reviewer: Akihiko Tsuchida, MD, PhD, Associate Professor, Department of Surgery, Tokyo Medical University, 6-7-1 Nishi-Shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan

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INTRODUCTION

Peritoneal dissemination of gastrointestinal (GI) or gynecologic cancers or primary peritoneal neoplasms constitute a difficult challenge for the practicing oncologist given the dismal prognosis associated with these entities and the debilitating effect that they exert on those patients who suffer them. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy is currently a valid treatment option for selected cases diagnosed with these diseases. Extensive clinical and pharmacological research studies have been conducted and unprecedented therapeutic results have been reported[1-4], bringing peritoneal surface oncology to the forefront of clinical oncology practice and research. Moreover, peritoneal surface malignancy treatment centers have been established around the world.

Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy is a complex therapeutic modality. It includes an aggressive and extensive surgical procedure and the administration of intraperitoneal chemotherapy, either in the intraoperative setting with hyperthermia or/and in the early postoperative setting. In expert hands, the associated morbidity and mortality parallels that of other major oncological surgery[5], but this expertise needs to be gained. Awareness of treatment-related toxicity is important and needs to be factored in the patient selection process.

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) is delivered in the operating room once the cytoreductive surgical procedure is finalized and constitutes the most common form of administration of perioperative intraperitoneal chemotherapy. The acronym HIPEC, coined by the group from the Netherlands Cancer Institute, became the standardized nomenclature for this procedure as a result of the experts' consensus achieved during the Fourth International Workshop on Peritoneal Surface Malignancy (Madrid, 2004)[6].

In this article, the rationale that supports its use and the methodology employed for the delivery of HIPEC are discussed. Additionally, safety precautions to be observed during the procedure are reviewed.

RATIONALE

The pharmacokinetic advantage of intraperitoneal chemotherapy administration

Following intraperitoneal delivery of cytotoxic drugs, high regional concentrations can be achieved while keeping systemic drug levels low. The concentration differential is in part due to the relatively slow rate of movement of the drug from the peritoneal cavity into the plasma (peritoneal clearance). This pharmacokinetic advantage is explained by the existence of a peritoneal-plasma barrier, which maintains a continuous high concentration gradient of chemotherapeutic drug between the peritoneal cavity and the plasma compartment[7,8], although its exact anatomical nature has not been fully elucidated. Actually, extensive removal of the diseased peritoneum during cytoreductive surgery does not seem to affect the pharmacokinetics of intraperitoneal chemotherapy[9]. An additional advantage to intraperitoneal chemotherapy administration is that the blood drainage of the peritoneal surface occurs *via* the portal vein to the liver, providing a first-pass (detoxifying) effect and an increased exposure of potential hepatic micrometastases to cytotoxic drugs[10]. Certain drugs are also transported through lymphatics to the systemic circulation and consequently higher drug concentrations in the lymph than in the plasma are achieved.

The area under the concentration-time curve ratio (AUC ratio) of the drugs between the peritoneal cavity and the peripheral blood expresses most adequately the pharmacological advantage of intraperitoneal drug administration. Depending on their molecular weight, their affinity to lipids and first-pass effect and clearance by the liver, the intraperitoneal to plasma drug AUC ratio may exceed 1000, as in the case of placlitaxel. Commonly used agents in GI or gynaecological oncology such as platinum derivatives, 5-FU, taxanes, irinotecan, adriamycin or mitomycin C show this advantage to a different extent.

The pharmacokinetic model that governs this phenomenon goes beyond the classical two-compartment model, with two compartments (plasma and peritoneal cavity in this case) separated by a semipermeable membrane. A three-compartment model that incorporates the tumor-bearing peritoneum as the third compartment, where the drug is also incorporated by tissue penetration, offers a more accurate explanation[11]. This compartment is the actual target of the cytotoxic treatment and can also be reached *via* systemic administration of the drug *via* subperitoneal capillaries; this provides the rationale for the recently designed "bidirectional" chemotherapy regimens consisting in the concurrent intraperitoneal and intravenous administration of the drugs.

Tissue penetration

A disadvantage of intracavitary chemotherapy is the limited tissue penetration by the therapeutic agent. Unfortunately, for many agents it is difficult to accurately measure tissue penetration depth and concentration after intraperitoneal administration and, when possible, there is a large inter-individual variation. Nevertheless, the penetration depth of drugs that are intraperitoneally delivered is estimated to be a maximum of 3 to 5 mm[12-17]. These figures are actually considered an overestimation, the reality being in the range from a few cell layers to a few millimeters. This is the reason why an adequate cytoreductive surgery should precede the intraperitoneal delivery of drugs and why 2.5 mm in largest diameter is considered the threshold for residual tumor nodule diameter if a cytoreduction is to be considered optimal ("complete cytoreduction").

Hyperthermia

There is an abundance of experimental and clinical evidence that indicate that malignant cells are selectively destroyed by hyperthermia in the range of 41 to 43℃. The cellular and molecular basis for this selectivity has been well studied[18-20]. While inhibited RNA synthesis and mitosis arrest are reversible and nonselective results of hyperthermia, an increase in the number of lysosomes and

lysosomal enzyme activity are selective effects in malignant cells. These heat-induced lysosomes are more labile in malignant cells and therefore result in increased destructive capacity. Furthermore, the microcirculation in most malignant tumours exhibits a decrease in blood flow or even complete vascular stasis in response to hyperthermia, which is in contrast to an increased flow capacity found in normal tissues[21]. This, in combination with depression or complete inhibition of oxidative metabolism in tumour cells subjected to hyperthermia and unaltered anaerobic glycolysis, leads to accumulation of lactic acid and lower pH in the microenvironment of the malignant cell. This effect is selective for malignant cells and may be due to the increased sensitivity of mitochondrial membranes in malignant cells. The increased acidity then increases the activity of the lysosomes which are increased in number. This results in accelerated cell death of the more fragile malignant cells subjected to hyperthermia[19] as compared to normal cells.

Thermal enhancement of cytotoxicity

The combination of heat and cytotoxic drugs frequently results in an increased cytotoxicity, beyond that predicted for an additive effect. The synergism between both kinds of treatment is dependent on several factors including increased drug uptake in malignant cells which is due to increased membrane permeability and improved membrane transport. There is also evidence that heat may alter cellular metabolism and change drug pharmacokinetics and excretion, both of which can increase the cytotoxicity of certain chemotherapeutic agents[22]. Additional factors include increased drug penetration in tissue, temperature-dependent increases in drug action and inhibition of repair mechanisms. In many cases, this enhancement of activity and penetration depth of drugs is already seen above 39-40℃[16,20,23,24].

The synergism of heat and drugs has been well documented, especially for selected chemotherapeutic agents used during HIPEC. Several agents have been shown to have an apparently improved therapeutic index and efficacy when used with hyperthermia in *in vitro* and *in vivo* experimental studies. Generally, the highest thermal enhancement ratios have been observed for alkylating agents such as melphalan, cyclophosphamide and ifosfamide[25]. Thermal enhancement of cytotoxicity has been shown for a variety of drugs, the most questioned today is that of the taxanes.

Uncontrolled hyperthermia may result in acute and late systemic side-effects. Actually central temperature rises during HIPEC. However, in HIPEC the heat is applied locoregionally and hence such an adverse effect of hyperthermia on drugs' toxicity is not, or in a much lesser extent, to be expected.

Choice of drug and drug dosaging for HIPEC

The choice of the chemotherapeutic drug is very important and certain aspects have to be considered. It is important for the agent to lack severe direct local toxicity after intraperitoneal administration. Moreover, the drug should have a well-established activity against the malignancy treated. Drugs that have to be metabolized systemically into their active form are inappropriate for intraperitoneal use. Whereas in instillation intraperitoneal chemotherapy all categories of active drugs can be used, in HIPEC procedures a direct cytotoxic agent (cell cycle-nonspecific) is needed[22].

Systemic exposure to intraperitoneally administered drugs inevitably occurs to a variable, limited extent and is responsible for their toxicity. In order to make this exposure and the subsequent toxicity predictable, standardized dosaging by body surface area of both the drug and the volume of the carrier solution to be employed are recommended. For the latter, some authors recommend 2 L/m^2[26], whereas others propose 1.5 L/m^2[27].

TECHNIQUE

HIPEC is delivered once tumor cytoreduction has been concluded and before any digestive reconstruction or diversion is made. The rationale for this timing in relation to GI tract reconstruction has to do with the opportunity of exposing bowel section lines to the chemotherapy solution in an effort to minimize the chance for anastomotic or staple line recurrence. Although this is the classical way to do it, there are some groups that perform anastomoses before the administration of HIPEC with no apparent increase in anastomotic recurrences.

The chemotherapy solution is prepared in the pharmacy department and it is sent to the operating room in a closed light-protected bag with appropriate labeling which is handled with double gloves and the integrity of the bag is checked. Any leak detected results in the bag being returned to the pharmacy department. If the bag is approved there is no risk of direct exposure and it is given to the person responsible for the perfusion, who must check the patient's name, drug and dose delivered against those prescribed.

Generally speaking, there are two methods for intraperitoneal administration of hyperthermic chemotherapy: open abdomen technique and closed abdomen technique.

The open method is usually performed by the "Coliseum technique", as described by Sugarbaker[28]. Once the cytoreductive phase has been finalized, a Tenckhoff catheter and four closed suction drains are placed through the abdominal wall and made watertight with a purse string suture at the skin. A different number of temperature probes secured to the skin edge may be used for intraperitoneal temperature monitoring; at least one in the in-flow line and another one at a distance from this point (pelvis) are employed. The skin edges of the abdominal incision are suspended up to a Thompson self-retaining retractor by a running monofilament number 1 suture, in order to create an open space in the abdominal cavity. A plastic sheet is incorporated into this suture to prevent chemotherapy solution splashing from occurring. A slit in the plastic cover is made to allow the surgeon´s double gloved hand access to the abdomen and pelvis.

Impervious gown and protection goggles are mandatory. The smoke evacuator is placed under the plastic sheet to clear chemotherapy particles that may be liberated during the procedure. During the 30 min to 90 min of perfusion, all the anatomic structures within the peritoneal cavity are uniformly exposed to heat and chemotherapy by continuous manipulation of the perfusate. A roller pump forces chemotherapy perfusion into the abdomen through the Tenckhoff catheter and pulls it out through the drains, with a flow rate around 1 L/min. A heat exchanger keeps the fluid being infused at 43-45℃ so that the intraperitoneal fluid is maintained at 41-43℃. The one-use circuit tubing is commercially available from the HIPEC machine companies or from the cardioplegia industry, and most of them incorporate a reservoir, useful when the chemotherapy solution needs to be quickly extracted from the abdomen for any complication or in cases where the perfusate volume calculated cannot be fully accommodated by the peritoneal cavity capacity. The perfusate is first recirculated between the reservoir and the heat exchanger so that it can be heated to an adequate temperature. At this point, full circulation of the perfusate in and out of the peritoneal cavity is established until a minimum intraperitoneal temperature of 41.5℃ is achieved and maintained. The drug is then added to the circuit and the timer for the perfusion is started. In the bidirectional chemotherapy protocols (sometimes referred to as "HIPEC-plus"), the intravenous infusion of the appropriate drugs is started at this time point as well, although some authors advocate doing it 1 h before the initiation of HIPEC.

The main benefit of the Coliseum technique is that heated chemotherapy is adequately distributed throughout the abdominal cavity and there is no pooling of temperature or chemotherapy. One disadvantage of the open technique is heat dissipation that makes it more difficult to initially achieve a hyperthermic state. Another possible disadvantage is the increased exposure of operating room personnel to chemotherapy. As the surgeon is manipulating chemotherapy throughout the perfusion, an increased potential for contact exposure exists. Furthermore, because the abdomen is open during the perfusion, heated chemotherapy could give way to aerosol formation, creating a risk of inhalation exposure. Stuart *et al*[29] evaluated the safety of operating room personnel during the Coliseum technique. Urine from members of the operating team was assayed for chemotherapy levels. Air below and above the plastic sheet was also analyzed. Finally, sterile gloves commonly used in the operating room were examined for permeability to chemotherapy. All assessments of potential exposures were found to be negative and in compliance with established safety standards.

Side effects from HIPEC appear to be principally related to the magnitude of the surgery[5]. The open technique has theoretical advantages over the closed technique due to improved distribution of heated chemotherapy; however, it has not been definitively proven in a randomized controlled trial.

A variation of the open technique described and mainly used in Japan uses a device called "peritoneal cavity expander" (PCE). The PCE is an acrylic cylinder containing in-flow and out-flow catheters that is secured over the wound. When filled with heated perfusate, the PCE can accommodate the small bowel, allowing it to float freely and be manually manipulated in the perfusate. After HIPEC is completed, the perfusate is drained and the PCE is removed. By using the expander, a more uniform distribution is theoretically achieved compared to a closed technique. The main disadvantage of the PCE technique is the risk of exposure to chemotherapy of the operating room personnel as in Coliseum technique[30]. Fujimura *et al*[30] reported about PCE-HIPEC use in carcinomatosis from various malignancies with good results. Yonemura *et al*[31] reported the use of the PCE-HIPEC technique for prophylaxis against recurrence of gastric cancer following resection with 5-year survival of 55% but only a 30% in surgery-only controls. Although there are no studies directly comparing PCE to the coliseum technique or closed technique, the reported results appear to be similar.

In the closed technique catheters and temperature probes are placed in the same fashion but the laparotomy skin edges are sutured watertight so that perfusion is done in a closed circuit. The abdominal wall is manually agitated during the perfusion period in an attempt to promote uniform heat distribution. A larger volume of perfusate is generally needed to establish the circuit compared with the open technique and a higher abdominal pressure is achieved during the perfusion, which may facilitate drug tissue penetration. After perfusion, the abdomen is reopened and the perfusate is evacuated. Appropriate anastomoses are performed and the abdomen is closed in the standard fashion.

A major advantage of the closed technique is the ability to rapidly achieve and maintain hyperthermia as there is minimal heat loss. In addition, there is minimal contact or aerosolized exposure of the operating room staff to the chemotherapy. The only way for exposure is leakage through the surgical wound or catheter wounds. The main disadvantage is the lack of uniform distribution of the chemotherapy. When methylene blue was instilled using closed technique, uneven distribution was observed. Uneven distribution of HIPEC is problematic, because hyperthermia has a narrow therapeutic index. Tumoricidal activity is manifested at 41-43℃; therefore in-flow temperature usually exceeds 45℃[32]. Rats exposed to intraperitoneal temperatures of 45℃ suffered significant morbidity and mortality[33]. Therefore, inadequate circulation of heated perfusate leads to pooling and accumulation of heat and chemotherapy in dependent parts of the abdomen. This may result in increased systemic absorption and foci of hyperthermic injury that could contribute to postoperative ileus, bowel perforation, and fistula. On the other hand, certain intraabdominal areas will be undertreated. Cytoreduction and HIPEC closed technique can be performed safely as it has been reported in different centers[34,35]. Morbidity associated with this procedure includes myelosuppression, ileus, and fistula, as in the open technique. Heterogeneous distribution inside the

closed abdomen may increase the rate of intra-abdominal complications.

In the last few years, increased interest in HIPEC has led to the commercial development of hyperthermic intraperitoneal perfusion systems. These are compact devices that contain roller pumps, a heating device, a heat exchanger and temperature monitors in a single apparatus. A computer integrates and displays information from the temperature probes, inflow and outflow rates. Several options are commercially available at this time.

The role of the anesthesiologist is crucial during HIPEC, as it is during the whole complex cytoreductive procedure. Specific training is desirable. During the whole lengthy surgical procedure knowledgeable fluid management needs to be carried out, keeping a balance between the use of crystalloids and colloids to achieve adequate central venous pressures and urine output without incurring in fluid overload. The latter is a common undesirable side effect observed after this surgery with consequences that range from acute pulmonary edema to cerebral edema when anesthesiologists not familiarized with this procedure are assigned to these cases. A minimal urine output of 100 cc (desirable 150 cc) every 15 min during the administration of HIPEC is mandatory to avoid renal toxicity derived from the cytotoxic drug employed. The utilization of a low-dose dopamine perfusion is a common measure to achieve this goal. Central temperature is monitored by an esophageal probe and may be expected to rise up to 39℃ or more; different cooling measures need to be implemented at this time to avoid sustained central hyperthermia starting by turning off the air heating blankets and moving to the intravenous administration of cold crystalloids or placement of ice packs around the head and neck of the patient.

HIPEC DRUG REGIMENS

Different drug regimens have been employed over the years for HIPEC. Drug choice primarily depends on its known activity against the disease being treated and its suitability for intraoperative administration with hyperthermia (cycle-non-specific method of action, heat-synergized cytotoxicity, non-vesicant). Single drug and drug combination regimens are currently in use. Although different carrier solutions with varying chemical properties have been investigated[36], 1.5% dextrose isotonic peritoneal dialysis solution is the most widely employed. Some groups use regular crystalloids (normal saline or 5% dextrose in water). Heavy molecular weight starch (6% Hetastarch®) is regularly employed as carrier solution for paclitaxel[37].

An important issue regarding toxicity of HIPEC has to do with dosaging. Both the drug dose and the carrier solution volume should be calculated based on body surface area, so that toxicity can be predictable. Perfusate volumes commonly used may be 1.5 L/m^2[26] or 2 L/m^2[27]. HIPEC regimens using fixed doses (same dose for any patient), drug dosaging by liter of perfusate or by body weight are more prone to find untoward events secondary to unnoticed overdosing of the cytotoxic drug employed. A 33% dose-reduction is recommended for patients over the age of 60, previously exposed to multiple lines of systemic chemotherapy, who needed GM-CSF rescue for febrile neutropenia while on systemic chemotherapy or who have received radiation therapy to bone-marrow bearing regions.

Perioperative intraperitoneal chemotherapy regimens that employ early postoperative intraperitoneal chemotherapy (EPIC) use moderate drug doses for HIPEC, while those that do not employ EPIC use much higher doses for HIPEC. In the last few years, bidirectional HIPEC regimens (concurrent administration of intraperitoneal and intravenous chemotherapy) have gained ground. Elias was first to use intravenous 5-FU and folinic acid prior to HIPEC with oxaliplatin due to the instability of the mix of both drugs[26]. Sugarbaker would later demonstrate that after the intravenous administration of 5-FU in a patient under general anesthesia in an intraperitoneal hyperthermic environment, the drug unexpectedly accumulates in the peritoneal cavity, a true heat-targeting phenomenon[11]. Table 1 lists commonly-used HIPEC regimens.

GUIDELINES FOR SAFE ADMINISTRATION OF HIPEC

Finally, safety measures in the operating room where HIPEC is to be administered cannot be overemphasized. Although chemotherapy is diluted in the carrier solution and the adverse effects of continuous exposure to low doses of cytotoxic drugs remain unknown, a breach in operating room safety that may unnecessarily expose the staff to hazardous drugs can destroy a HIPEC treatment program. Certain general safety measures must be in effect every tine HIPEC is used in the operating room[38]: (1) At the beginning of the operation the surgical field should be arranged with impervious, disposable sheets and drapes, avoiding the use of any non-disposable fabric cloth; (2) After cytoreduction, all staff not directly involved in the administration of HIPEC should leave the operating room during the administration of the treatment and staff circulation in and out of the room should be kept to a minimum; (3) Signs warning that HIPEC is in progress must be placed at the entrance of the dedicated surgical area; (4) Absorbent towels with impervious back are placed on the floor and all around the surgical table for possible spills; (5) Rigid containers, leak proof for biologically hazardous material and properly labeled with "cytotoxic agents" labels, are placed in the operating room. They should not be more than half full. Chemotherapy contaminated material should be handled as little as possible and with minimal agitation to prevent dissemination into the environment; (6) Protective barrier garments should be worn for all procedures involving preparation, use and disposal of cytotoxic drugs. In the operating room, during HIPEC, all personnel should wear protective disposable impervious gowns and shoe covers, non-permeable powderless latex

Table 1 Common HIPEC regimens currently in use

Center/Country	HIPEC drug (s) and doses	HIPEC duration (min)	Concomitant intravenous chemotherapy	EPIC	Indication
Washington hospital center/ Washington, DC (USA)	Mitomycin C, 15 mg/m^2 Doxorubicin, 15 mg/m^2	90	5-FU, 400 mg/m^2 LV, 20 mg/m^2	5-FU 4 d	Appendiceal, and colorectal carcinomatosis
Washington hospital center/ Washington, DC (USA)	Cisplatin, 50 mg/m^2 Doxorubicin, 15 mg/m^2	90	5-FU, 400 mg/m^2 LV, 20 mg/m^2	Taxol 4 d	Gastric cancer, peritoneal mesothelioma, ovarian cancer
Washington hospital center/ Washington, DC (USA)	Oxaliplatin, 130 mg/m^2	60	5-FU, 400 mg/m^2 LV, 20 mg/m^2	5-FU 4 d	Appendiceal, and colorectal carcinomatosis
Washington hospital center/ Washington, DC (USA)	Melphalan, 50-70 mg/m^2	60	No	No	Carcinomatosis with incomplete cytoreduction
Gustave roussy institute/ Villejuif (France)	Oxaliplatin, 460 mg/m^2	30	5-FU, 400 mg/m^2 LV, 20 mg/m^2	No	Colorectal carcinomatosis
National cancer institute/ Amsterdam (Netherlands)	Mitomycin C, 35 mg/m^2	90	No	No	Appendiceal, and colorectal carcinomatosis
National cancer institute/ Milan (Italy)	Cisplatin, 43 mg/L Doxorubicin ,15.25 mg/L	90	No	No	Peritoneal mesothelioma, advanced ovarian cancer
National cancer institute/ Milan (Italy)	Mitomycin C, 3.3mg/m^2/L Cisplatin, 25 mg/m^2/L	90	No	No	Appendiceal, and colorectal carcinomatosis; advanced ovarian cancer; peritoneal mesothelioma
Centre hospitalo-universitaire lyon-sud/Lyon (France)	Mitomycin C, 10 mg/mL of perfusate	90	No	No	Appendiceal, gastric and colorectal carcinomatosis
Centre hospitalo-universitaire lyon-sud/Lyon (France)	Mitomycin C, 0.5 mg/kg Cisplatin 0.7 mg/kg	90	No	No	Peritoneal mesothelioma
Centre hospitalo-universitaire lyon-sud/Lyon (France)	Cisplatin, 20 mg/m^2/L	90	No	No	Recurrent and chemoresistant stage Ⅲ ovarian cancer
National cancer institute/ Bethesda, MD (USA)	Cisplatin, 250 mg/m^2	90	No	5-FU + Taxol 1 d	Peritoneal mesothelioma

L: liter of perfusate; HIPEC: Hyperthermic intraperitoneal chemotherapy; EPIC: Early postoperative intraperitoneal chemotherapy.

gloves worn as double gloves and eye wear for possible droplet protection. Potentially contaminated garments must not be worn outside the work area; (7) Universal Precautions for handling biological hazardous materials are implemented and monitored continuously. Any body fluid, blood sample, tissue specimen, laparotomy pads, drapes, gowns or plastic tubing must be handled as biological hazardous material. Body fluids are considered contaminated for 48 h after the last administration of chemotherapy. Labels saying "cytotoxic agent" should be used to mark every sample, specimen, or contaminated trash; (8) Latex powder-free gloves are recommended for all procedures involving cytotoxic drugs. They should be non-permeable and worn as double gloves for direct contact with chemotherapy. In a comparative study, Biogel™ gloves were found to have the lowest permeability to chemotherapy[29]. Gloves should be routinely changed approximately every 30 min when working steadily with cytotoxic agents. Gloves should be changed immediately after overt contamination. Double gloving is recommended for cleaning up of spills. Surgeons in direct contact with chemotherapy should wear the outer glove up to the elbow (Figure 1) ; (9) High power filtration mask (FFP-3) tightly fit to the face (high filtration of sub-micron particles) may be recommended at some centers; (10) A smoke evacuator should be working continuously under the plastic sheet during the perfusion; (11) Every effort should be done to avoid any spill, but if it happens, the circulating nurse should contain and clean it up immediately. If direct contact with a cytotoxic agent occurs, contaminated clothing should be removed immediately and discarded in a hazardous waste container. Affected skin should be washed immediately with mild, additive-free soap with no dyes or perfumes that may interact with the cytotoxic agent. If the affected area is the eye, it should be flooded immediately with water or isotonic saline for 5 min. The staff member should then report the incident to the occupational health office. The area should be washed three times with water and neutral soap. Then, the area can be cleaned in the routine manner. To clean up a small spill, the personnel should wear the whole protective barrier garments already described. A large spill is defined as a drop of more than 5 g or 5 mL of pure drug. Personnel containing the spill should wear a respirator mask and standard protective clothing. They should take care to avoid creating aerosols when cleaning large spills; (12) During HIPEC and EPIC, chemotherapy is always diluted, never pure, and doses

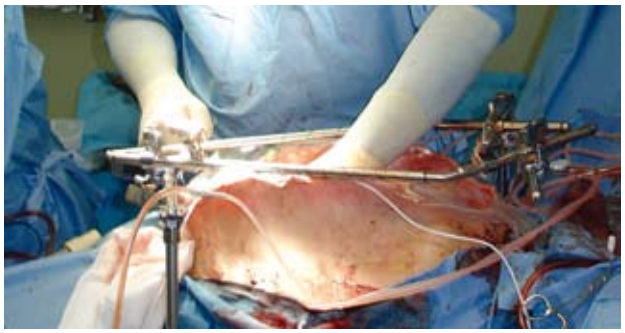

Figure 1 Administration of HIPEC by the coliseum (open) technique. Constant manipulation of the perfusate ensures a homogeneous distribution of the heated chemotherapy within the peritoneal cavity. Note that elbow-length double gloving, goggles and an impervious gown are used.

of drugs are in micrograms, so that it is not possible to have a major spill; (13) Cleaning the operating room after HIPEC: personnel should wear the standard protective clothing described. Bactericidal cleaning solutions should not be used to wash contaminated area because they may react with the cytotoxic agents and do not inactivate them. Water with neutral soap is adequate to clean the operating room after HIPEC three consecutive times. Seventy percent isopropyl alcohol is also safe and effective; and (14) Instrument trays are labeled with "cytotoxic agent". They should be washed three times with water and pure soap before leaving the working area.

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TOPIC HIGHLIGHT

Antonio Macrì, MD, Professor, *Series Editor*

Experience with peritoneal mesothelioma at the Milan National Cancer Institute

Marcello Deraco, Dario Baratti, Antonello Domenico Cabras, Nadia Zaffaroni, Federica Perrone, Raffaella Villa, Jenny Jocollè, Maria Rosaria Balestra, Shigeki Kusamura, Barbara Laterza, Silvana Pilotti

Marcello Deraco, Dario Baratti, Maria Rosaria Balestra, Shigeki Kusamura, Barbara Laterza, Department of Surgery, National Cancer Institute, 20133 Milan, Italy
Antonello Domenico Cabras, Federica Perrone, Jenny Jocollè, Silvana Pilotti, Department of Pathology, National Cancer Institute, 20133 Milan, Italy
Nadia Zaffaroni, Raffaella Villa, Department of Experimental Oncology, National Cancer Institute, 20133 Milan, Italy
Author contributions: Deraco M, Baratti D, Kusamura S, Zaffaroni N and Pilotti S designed the research; Deraco M, Baratti D, Cabras AD, Perrone F and Villa R wrote the paper; Jocollè J, Balestra MR and Laterza B contributed to collect the data.
Correspondence to: Marcello Deraco, MD, Department of Surgery, National Cancer Institute, Via Venezian,1 20133 Milan, Italy. marcello.deraco@istitutotumori.mi.it
Telephone: +39-2-23902362 Fax: +39-2-23902404
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Abstract

Diffuse malignant peritoneal mesothelioma (DMPM) is an uncommon and rapidly fatal tumor. Therapeutic options have traditionally been limited and ineffective. The biologic and molecular events correlated with poor responsiveness to therapy are still poorly understood. In recent years, an innovative treatment approach involving aggressive cytoreductive surgery (CRS) and perioperative intraperitoneal chemotherapy has reportedly resulted in improved outcome, as compared to historical controls. Since 1995, at the National Cancer Institute (NCI) of Milan (Italy), patients with DMPM have been treated with CRS and hyperthermic intraperitoneal chemotherapy (HIPEC). In the present paper, clinical experiences and basic science investigations on DMPM at Milan NCI are reviewed. Perioperative and long-term outcome results with CRS and HIPEC are presented. Clinico-pathological prognostic factors were investigated by multivariate analysis. The pathologic features and immunohistochemical markers related to DMPM biologic behavior were assessed in a large case-series uniformly treated at our institution. The prevalence and prognostic role of telomere maintenance mechanisms, which account for the limitless cell replicative potential of many malignancies, were studied. The dysregulation of the apoptotic pathways may play a role in the relative chemo-resistance of DMPM and a better understanding of apoptosis-related mechanisms could result in novel targeted therapeutic strategies. On this basis, the expression of survivin and other IAP family members (IAP-1, IAP-2, and X-IAP), the pro-apoptotic protein Smac/DIABLO, and antigens associated with cell proliferation (Ki-67) and apoptosis (caspase-cleaved cytokeratin-18) were analyzed. Finally, analyses of *EGFR*, *PDGFRA* and *PDGFRB* were performed to ascertain if deregulation of RTK could offer useful alternative therapeutic targets.

Key words: Peritoneal mesothelioma; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Telomerase; Surviving; Apoptosis; Receptor tyrosin kinase

Peer reviewers: Stephen Randolph Grobmyer, MD, Assistant Professor, Division of Surgical Oncology, Department of Surgery, University of Florida, 1600 SW Archer Rd., PO Box 100286, Gainesville, FL 32610, United States; Maria Gazouli, PhD, Department of Biology, School of Medicine, University of Athens, Michalakopoulou 176, Athens 11527, Greece

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INTRODUCTION

Malignant mesothelioma is an uncommon tumor arising from the serosal layer of pleura, peritoneum, pericardium and tunica vaginalis testis[1]. The incidence of the disease has been rising worldwide since 1970, due to widespread exposure to asbestos during previous decades, and it is not expected to peak before the next 20 years[2]. In the United States, approximately 2500 new cases of mesothelioma are registered each year. Diffuse malignant peritoneal mesothelioma (DMPM) accounts for 10% to 30% of all mesotheliomas[3].

In historical case-series, standard therapy with palliative surgery and systemic or intraperitoneal chemotherapy is associated with a median survival of about one year, ranging from 9 to 15 mo[4-6]. However, the disease tends to remain within the abdominal cavity throughout its clinical course and an autopsy study demonstrated that 78% of patients had died because of complications directly related to local-regional progression[7].

In recent years, this has prompted a few specialized centers to develop an innovative local-regional treatment approach. It involves cytoreductive surgery (CRS) with peritonectomy procedures and multivisceral resections to remove the entire visible tumour. Microscopic residual disease is treated by perioperative intraperitoneal chemotherapy. This comprehensive strategy has reportedly resulted in a median survival of 34-92 mo, which strongly suggests improved outcome as compared to historical controls[8-14].

At the National Cancer Institute (NCI) of Milan (Italy), the first combined procedure of CRS and hyperthermic intra-peritoneal chemotherapy (HIPEC) was performed in February 1995 in a patient with peritoneal carcinomatosis from ovarian cancer. In August 1995, the first patient with peritoneal mesothelioma, which was the tenth of the overall series, was treated. The present paper reviews our institutional experience with a special focus on clinical results, pathological studies and basic science investigations.

DIAGNOSIS OF PERITONEAL MESOTHELIOMA

The histologic features of malignant peritoneal mesothelioma are sub-divided into epithelial, sarcomatoid, and biphasic tumors. Clinical and pathological diagnosis of mesotheliomas can be very difficult. The morphology of the neoplasm is extremely variable and is a major basis for diagnostic dilemma[15]. Malignant mesotheliomas are difficult to distinguish from benign reactive lesions of the pleura as well as from metastatic adenocarcinomas. Immunohistochemical studies represent a very important diagnosis aid. At present, however, an absolutely specific marker for mesothelioma has not yet been recognized and the immunohistochemical diagnosis of this tumor largely depends on the use of panels of markers that combine positive [thrombomodulin (CD141), calretinin, keratin 5/6, D2-40, podoplanin, mesothelin, and Wilms tumor 1 protein (WT1)] with negative markers (carcinoembryonic antigen, MOC-31, B72.3, and Ber-EP4) most commonly present in carcinoma[16]. Thyroid transcription factor 1 (TTF-1) can assist in determining origin from lung carcinoma, CDX-2 origin from colon carcinoma, CK 7 and Claudin 4 origin from ovarian carcinoma. Renal cell carcinoma marker (RCC Ma) may be helpful in establishing renal origin. Claudin 4 is a transmembrane protein component of tight junctions, responsible for cell adhesion. Claudin 4 identifies a wide spectrum of epithelial neoplasms and represents a very useful marker for carcinoma *vs* mesothelioma diagnosis in pleural and peritoneal biopsies and effusions. D2-40 is a commercially available monoclonal antibody that reacts with a 40 kDa antigen in fetal germ cells and germ cell tumors. Since the antibody reacts with epithelial mesotheliomas, but not with carcinomas, it could be very helpful in discriminating between these malignancies. Podoplanin is an approximately 38 kDa membrane mucoprotein originally detected on the surface of rat glomerular epithelial cells (podocytes) that is specifically expressed in the endothelium of lymphatic capillaries but not in the blood vasculature. Podoplanin, like D2-40, is expressed in mesotheliomas but not in adenocarcinomas. Calretinin is an intracellular calcium-binding protein belonging to the troponin C superfamily. At present, calretinin is regarded as being the most sensitive and one of the most specific mesothelioma markers. Calretinin is frequently expressed in both histologic types of mesothelioma, i.e. epithelial and sarcomatoid.

WT1 was first described in 1990 as a tumour suppressor gene associated with Wilms tumour (nephroblastoma). It encodes a typical transcription factor with four C_2-H_2 zinc fingers in the C-terminus that is expressed in mesotheliomas but not in adenocarcinomas. Because of its high sensitivity and absolute specificity, *WT1* is one of the best positive markers for discriminating between metastatic adenocarcinomas and mesotheliomas. The vast majority of cases of squamous cell carcinoma, basal cell carcinoma, thymoma, salivary gland tumor, and biphasic malignant mesothelioma were positive for CK 5/6. CK 5/6 has been used to distinguish malignant mesothelioma from adenocarcinoma of the lung. Thrombomodulin (CD141) is a glycoprotein of molecular weight 75000 kD that is normally present in restricted numbers of cells, including endothelial and mesothelial cells, and was the first of the positive mesothelioma markers that proved useful in the diagnosis of this tumor.

TREATMENT PROTOCOL

Cytoreductive surgical procedures are performed with the aim of removing all the peritoneal tumor deposits according to the technique described by Sugarbaker[17].

In the first 11 patients, HIPEC was administered with cisplatin (25 mg/L of perfusate/m^2) and mitomycin-C (3.3 mg/L of perfusate/m^2) for 60 min.

From June 1997 to December 1999, patients with DMPM were included in a multi-institutional phase I study testing the combination of cisplatin and

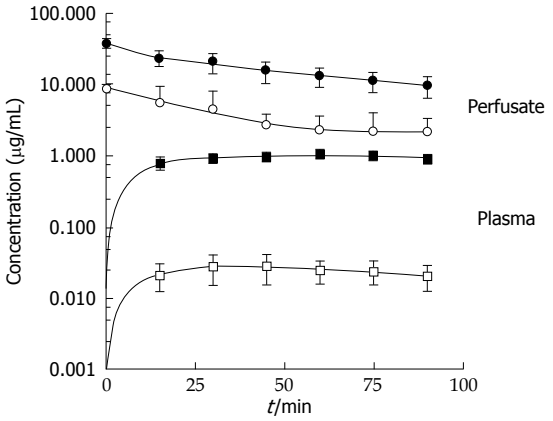

Figure 1 Time courses of the mean concentrations of doxorubicin and cisplatin in perfusate and plasma. Solid lines obtained by nonlinear least squares regression analyses of data. Open symbols: Doxorubicin (DXR); Filled symbols: Cisplatin (CDDP).

doxorubicin in the local-regional setting[18]. Doxorubicin was chosen due to its clinical activity against mesothelioma (as well as ovarian carcinoma and soft-tissue sarcoma), its favourable plasma/peritoneal ratio and high molecular weight, allowing a more rapid clearance from normal than from tumour tissue[19-21]. Doxorubicin activity is also synergistically enhanced by heat and cisplatin, thus favouring its use in a combination regimen under hyperthermic conditions.

Thirty one patients with liposarcoma (n = 9), leiomyosarcoma (n = 6), other soft-tissue sarcomas (n = 4), ovarian carcinoma (n = 6), and malignant mesothelioma (n = 6) undergoing adequate CRS (residual tumour ⩽ 2.5 mm) constituted the study population. HIPEC was performed for 90 min at a mean intraperitoneal temperature of 42.5℃. The drugs were administered to triplets of patients in escalating doses, starting with 5 and 20 mg/L of perfusate for doxorubicin and cisplatin, respectively. The dose was increased by 25% for each subsequent triplet. Accrual was stopped when grade Ⅳ loco-regional toxicity was observed in one patient. The maximal tolerated dose (MTD) was considered to be that of the previous triplet and was confirmed after three more patients had been treated uneventfully with the putative MTD.

One patient treated with 19 mg/L of doxorubicin and 43 mg/L of cisplatin experienced Grade Ⅳ loco-regional toxicity (persistent ileus) and required reoperation. To confirm that MTD had been reached, we treated three more patients with the previous triplet drug dosages. Because no significant loco-regional toxicity was observed, MTD was established at 15.25 mg/L of doxorubicin and 43 mg/L of cisplatin.

The results of the pharmacokinetic studies are illustrated in Figure 1, which clearly shows how similar perfusate concentrations of doxorubicin and cisplatin gave very different plasma concentrations, with doxorubicin levels being roughly 50-fold lower.

CLINICAL RESULTS

The clinical results from the Milan NCI were published in a preliminary report of the first 20 cases[22], a clinico-pathological study[23], an extensive prognostic analysis of potential clinical, pathological and biological variables[24], and an assessment of the pattern of failure[25].

Forty-nine patients with DMPM were enrolled to test the association between potential prognostic variables and survival by multivariate statistical analysi[24]. Patients with low malignant variants (multicystic and papillary well-differentiated mesothelioma) were excluded. The mean age was 52 years (range 22-74 years). Twenty-six patients had preoperative systemic chemotherapy. Forty-three patients were diagnosed with epithelial and 6 patients with biphasic DMPM; 43 patients underwent complete cytoreduction (residual tumor ⩽ 2.5 mm) and 6 patients underwent grossly incomplete cytoreduction.

At a mean follow-up of 20.3 mo (range 1-89 mo), the 5-year overall survival (OS) and progression-free survival (PFS) were 57% and 31%, respectively. The median PFS and OS were 39.7 mo and not reached, respectively. There were no treatment-related deaths. Grade 3-4 (NCI CTCAE v.3) surgical complications occurred in eight cases (15%) and grade 3-4 toxicities in six cases (12%).

Potential prognostic variables with P values < 0.20 at univariate analysis (log-rank test), were included in the Cox proportional hazard model (Table 1). The backward-elimination method identified the completeness of cytoreduction and mitotic count (MC) > 5/50 HPF as independent predictors of OS, performance status and MC correlated to PFS.

The estimated hazard rate for patients with grossly incomplete cytoreduction was eight times higher than for those with optimal cytoreduction, after adjustment for other variables. This is in agreement with experimental evidence that intraperitoneal chemotherapy cannot penetrate tumour tissue deeper than a few millimeters. Thus, the volume of residual disease is one the major factors limiting the effectiveness of loco-regional therapy[8-14]. The second variable that remained in the Cox model as a factor influencing OS was MC. Patients with MC > 5/50 HPF presented a hazard rate 10 times higher, as compared with those with lower MC. Available data are conflicting: patients with high MC have been associated with poor prognosis[14], although other authors did not reach the same conclusion[26].

The preoperative clinical conditions have been shown to be a prognostic factor in pleural mesothelioma[1,2]. In the present series, the independent association between MC and PFS emerged after the multivariate analysis even in the absence of significant correlation by univariate analysis. However, the performance status did not correlate with OS. This could be explained by the small number of deaths and the fact that 89% of patients had a good performance status.

Despite encouraging survival results, approximately 40%-60% of patients developed disease progression and died of DMPM following comprehensive treatment[8-14]. However, data on patients who failed to respond to initial treatment are lacking and optimal management of recurrent DMPM has never been defined. Therefore, we

Table 1 Clinicopathologic variables with prognostic significance according to univariate (log-rank) and multivariate (Cox proportional hazard model) analyses

Variable	Overall survival			Progression-free survival		
	Univariate	Multivariate		Univariate	Multivariate	
	P value	HR (95% CI)	*P* value	*P* value	HR (95% CI)	*P* value
Sex	0.22			0.27		
Age (< 52 yr *vs* ⩾ 52 yr)	0.93			0.49		
Performance status (0 *vs* 1, 2, or 3)	0.43			0.05	0.29 (0.1-0.8)	0.02
Previous surgical score (0 *vs* ⩾ 1)	0.78			0.11		
Previous systemic CT	0.59			0.57		
PCI (⩾ 28 *vs* < 28)	0.12			0.10		
Completeness of cytoreduction (0/1 *vs* 2/3)[a]	0.01	8.6 (2.1-36.2)	0.00	0.08		
IPHP drug schedule (CDDP + DX *vs* CDDP + MMC)	0.36			0.98		
Histological subtype (epithelioid *vs* biphasic)	0.09			0.07		
Mitotic count(< 5 *vs* ⩾ 5)	0.01	10.5 (1.9-55.2)	0.01	0.19	3.1 (1.1-8.8)	0.03
Nuclear grade (high *vs* low)	0.02			0.10		

[a]0/1, minimal residual disease or residual tumor < 2.5 mm; 2/3, residual tumor ⩾ 2.5 mm. CI: Confidence interval; PCI: Peritoneal Cancer Index; IPHP: Intraperitoneal hyperthermic perfusion; CDDP: Cisplatin; DX: Doxorubicin; MMC: Mitomycin C; HPF: High-power field.

analysed the patterns of failure to understand how and possibly why combined treatment failed and to identify the modifications that might improve clinical results in a subset of 38 patients who developed disease progression following CRS and HIPEC[25].

Initial treatment consisted of adequate cytoreduction with residual tumour ⩽ 2.5 mm and HIPEC in 28 patients and grossly incomplete CRS in 10 patients. Detailed information regarding progressive disease distribution was prospectively collected by CT scan (n = 26) or both CT-scan and laparatomy (n = 12).

Median time-to-progression was 9 mo. In the individual patients, the pattern of failure was categorized as liver metastases (n = 1), involvement of celiac (n = 1) and retroperitoneal (n = 1) lymph-nodes, isolated seeding of the basal pleura (n = 2) and involvement of both abdominal and pleural cavity (n = 2). In the remaining 31 patients (81.6%), only peritoneal progression was noted: the small bowel and its mesentery were involved in 13 patients, intra-abdominal sites exclusive of small bowel in 4 patients, and both the small bowel and additional intra-abdominal sites in 14 patients. Overall, small bowel was involved in 27 patients (71.1%).

In 28 patients undergoing complete CRS, potential factors determining disease progression were statistically assessed in 13 distinct abdominopelvic regions. At multivariate analysis, only residual tumour up to 2.5 mm *vs* macroscopically complete CRS correlated to disease progression in the epigastric region, upper jejunum, lower jejunum and upper ileum. Taken together, these data strongly suggest that failure to remove the entire visible tumor in critical areas where cytoreductive surgery is technically difficult may be the leading cause of treatment failure. Therefore, maximal surgical efforts aiming at leaving behind no residual disease are an absolute requirement.

Progressive disease was treated with second HIPEC (n = 3), debulking (n = 4), systemic chemotherapy (n = 16), and supportive care (n = 15). Median survival from progression was 8 mo. At multivariate analysis, time-to-progression < 9 mo, poor performance status, and supportive care correlated with reduced survival from progression. Furthermore, operative treatment (i.e. cytoreduction or cytoreduction with HIPEC) showed a trend toward better outcomes, compared with systemic chemotherapy. Since treatment was determined according to patient conditions and disease extent, the different treatment modalities cannot be compared. Nevertheless, encouraging results were obtained with repeated cytoreduction and HIPEC, making aggressive treatment of progressive disease an attractive option.

MULTICYSTIC AND WELL-DIFFERENTIATED PAPILLARY PERITONEAL MESOTHELIOMA (WDPPM)

Multicystic peritoneal mesothelioma (MPM) and WDPPM are exceedingly uncommon lesions with uncertain malignant potential and no uniform treatment strategy[26,27]. From the beginning of our peritoneal malignancies treatment program, MPM and WDPPM were included among the indications to cytoreduction and HIPEC, owing to their known potential to relapse and to evolve into aggressive malignant tumours[28].

Twelve female patients (4 with MPM and 8 with WDPPM) underwent 13 combined procedures at the NCI of Milan. Seven patients had recurrent disease after previous debulking (1 operation in 5 patients, 2 in 1 patient, 4 in 1 patient). Due to their perceived low aggressiveness, small tumour deposits on visceral peritoneum were preferably removed by electrosurgical dissection and organ resections were performed only if massive disease involvement precluded a conservative approach. Accordingly, uteri and ovaries were spared in four reproductive age women and to date no recurrence has involved the pelvis. Optimal cytoreduction with no or minimal (⩽ 2.5 mm) residual disease was accomplished in 12 of 13 procedures (92.3%).

After a median follow-up of 27 mo (range 6-94 mo), postoperative disease progression occurred in two pa-

Table 2 Immunohistochemical results

Score	No. of patients (*n*)							
	Calretinin	WT-1	pCEA	Ber-Ep4	EGFR	p16	MMP-2	MMP-9
0	0	0	35	35	2	14	0	5
+1	0	5	0	0	1	11	2	9
+2	1	6	0	0	3	6	3	8
+3	6	5	0	0	7	2	7	8
+4	28	19	0	0	22	2	23	5

The immunohistochemistry stains were scored as 0 (negative), +1 (< 25%), +2 (25%-50%), +3 (50%-75%), and +4 (75%-100%). pCEA: Pathologic carcinoembryonic antigen; EGFR: Epidermal growth factor receptor; MMP: Matrix metalloproteinase.

tients and tumour-related death in one. The first patient underwent the procedure twice due to loco-regional MPM recurrence and is presently disease-free. Transition of typical WDPPM to malignant biphasic mesothelioma was documented in the second patient who died of disease progression following incomplete cytoreduction and HIPEC. Projected 5-year overall and progression-free survival were 90.0% and 79.7%, respectively. The projected progression-free survival after 11 debulking operations carried out in seven patients before referral to our center was 9.1% (SE = 6.1); the difference was statistically significant ($P = 0$ .0156).

Based on our findings, definitive tumour eradication by means of peritonectomy procedures and HIPEC is recommended as the optimal treatment to prevent either disease recurrence or transition to a truly aggressive tumour[28].

PATHOLOGICAL EVALUATION

The pathologic features of 35 patients with DMPM uniformly treated with CRS and HIPEC at the Milan NCI were assessed[23]. The hematoxylin and eosin-stained slides of all cases were reviewed and tumors were classified as epithelial, sarcomatoid, and biphasic (mixed epithelial and sarcomatoid)[29]. Nuclear grade (NG) was assessed as follows: Grade 1: small nuclei, uniform chromatin pattern, and small pinpoint-sized nucleoli; Grade 2: larger nuclei, some chromatin irregularity, and more prominent nucleoli; and Grade 3: large nuclei, irregular chromatin pattern with clearing, and prominent nucleoli[30]. Immunohistochemical studies using the avidin-biotin-complex immunoperoxidase technique were performed with the following antibodies: matrix metalloproteinase-2 (MMP-2); MMP-9; calretinin; WT-1; carcinoembryonic antigen (CEA); Ber-EP4; p16; and epidermal growth factor receptor (EGFR).

The immunohistochemical results are summarized in Table 2. EGFR was diffusely and strongly expressed in a membranous pattern in all but 2 cases (94%). Conversely, p16 was completely negative in 14 cases (40%) and only focally positive in 11 (31%). MMP-2 was expressed in all cases in a diffuse and strong fashion, whereas MMP-9 was expressed in 30 cases but with only variable intensity and distribution. Calretinin and WT-1 were expressed in all cases to a variable degree. Expression of polyclonal CEA and Ber-EP4 were negative in all cases.

In agreement with previous reports, p16 was absent or reduced in most DMPM cases[29]. Alterations of the *p16INK4* locus in patients with mesothelioma are relatively common. The recent molecular genetic study of 45 cases of primary mesothelioma revealed alterations of p16 in 31% of cases, promoter methylation in 9%, deletion in 22%, and point mutation in 2%[31]. Similar to many other cancers, DMPM exhibits altered cell-growth regulation involving the loss of *pRb* and *p53* function. Inhibition of the *p53*-dependent and *pRb*-dependent growth regulatory pathways may occur through mechanisms involving either homozygous loss of the *CDKN2A* (*p16INK4a/p14ARF*) locus at chromosome 9p21 or expression of SV40 Tag[32].

In the current study, 63% of cases demonstrated diffuse and strong immunoreactivity for EGFR, analogously to a previous report[33]. EGFR, a receptor tyrosine kinase, is reportedly over-expressed in a wide variety of malignancies. EGFR signaling leads to an increase in cellular proliferation, cell motility, angiogenesis, the inhibition of apoptosis, and the expression of extracellular matrix proteins. High levels of EGFR expression are associated with a poor prognosis in some malignancies.

Asbestos, which is associated with the development of mesothelioma, was reported to stimulate the EGFR auto-phosphorylation in mesothelial cells, trigger the extracellular-regulated kinase (ERK) cascade, and lead to increases in AP-1 activity[34]. In addition, DMPM cell lines are reported to express EGFR and transforming growth factor-α (TGF-α), suggesting an autocrine role for EGFR in DMPM[35].

Proteolytic degradation of the extracellular matrix and basement membranes by proteases is a key component of tumour cell invasion and metastasis. Overexpression of MMPs, particularly MMP-2 (gelatinase A), MMP-9 (gelatinase B), and MMP-11 (stromelysin-3), is related to tumor progression and metastasis in various malignancies[36,37]. MMP-2 and MMP-9 are key enzymes for degrading Type Ⅳ collagen, a major component of basement membranes, and are particularly expressed in mesenchymal-derived tumor cells[38]. To our knowledge, only a few studies have investigated MMP immunohistochemically on surgical specimens of DMPM[39].

BIOLOGIC PROGNOSTIC FACTORS

One of the hallmarks of cancer cells is their limitless replicative potential[40]. In a high percentage of tumors,

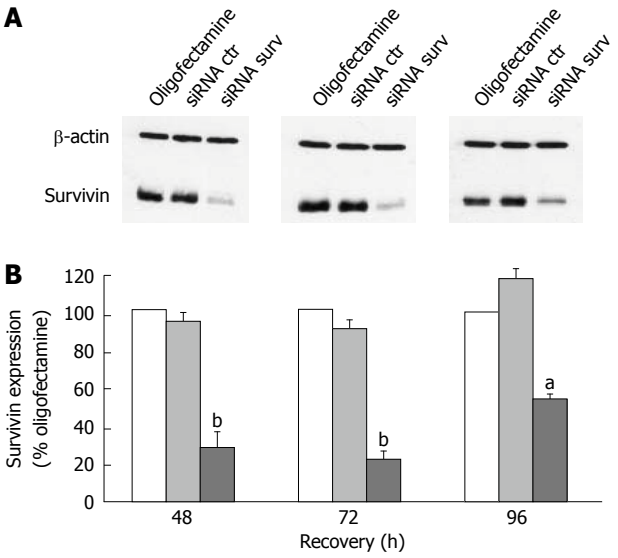

Figure 2 Representative Western blotting experiments illustrating survivin expression in STO cells exposed to oligofectamine alone or transfected with control siRNA and survivin siRNA. A: β-actin was used as a control for protein loading; B: Densitometric quantification of survivin band intensities in oligofectamine-exposed cells (empty column) and cells transfected with the control siRNA (gray column) or the survivin siRNA (black column). Data represent mean ± SD of 3 independent experiments. $^{a}P < 0.02$; $^{b}P < 0.01$; Student's *t* test; such inhibition was highest (around 80%; $P < 0.01$) at 48 h and 72 h after transfection and still appreciable, although to a lesser extent (around 50%; $P < 0.02$), at 96 h.

the attainment of immortality is due to the re-activation of telomerase, an RNA-dependent DNA-polymerase that stabilizes telomeres and allows tumour cells to avoid senescence[41]. Some tumors, however, do not have telomerase activity (TA) and maintain their telomeres by one or more mechanisms referred to as alternative lengthening of telomeres (ALT)[42]. No information is available thus far concerning the presence of telomere maintenance mechanism (TMM) in DMPM[43].

The prevalence and prognostic role of the two known TMM, TA and ALT, were investigated for the first time in a series of patients treated at the Milan NCI. Forty-four lesions from 38 patients undergoing CRS and HIPEC (n = 29) or debulking surgery (n = 9) were available[44]. TA was determined using the telomeric-repeat amplification protocol (TRAP) assay[45] and ALT by detecting ALT-associated promyelocytic leukemia (PML) nuclear bodies (APB). APB are sub-nuclear structures containing telomeric DNA, telomere-specific binding proteins and proteins involved in DNA recombination and replication[46].

Thirty-eight lesions (86.4%) expressed at least one TMM. Specifically, 28 lesions (63.6%) were TA+/ALT-, 8 (18.2%) were TA-/ALT+, and 2 (4.6%) were ALT+/TA+. The remaining 6 lesions (13.6%) did not express any TMM.

After a median follow-up of 38 mo (range 2-94 mo), TA correlated at multivariate analysis to both disease-free [TA+ *vs* TA-: 10% *vs* 64%; hazard ratio (HR) = 3.30; 95% Confidence Interval (CI): 1.23-8.86; $P = 0.018$] and cancer-related survival (TA+ *vs* TA-: 32% *vs* 79%; HR = 3.56; 95% CI: 1.03-12.51; $P = 0.045$). These results were confirmed also for the 29 patients who underwent CRS and HIPEC: patients with TA+ tumours had a significantly lower probability of being disease-free than patients with TA- tumours (HR = 3.32; 95% CI: 1.09-10.12; $P = 0.03$), and showed a trend toward better overall survival (HR = 3.69; 95% CI: 0.79-17.13; $P = 0.09$) (Figure 1). ALT failed to significantly affect clinical outcome both in the overall series and in the subset of patients undergoing CRS and HIPEC (Figure 2).

Table 3 Staining characteristics for IAP family members, Smac/DIABLO, apoptotic and proliferation indices in peritoneal mesothelioma

	Positive cases (n)	Median expression (range, %)
Survivin, full length[1]	26	60 (0-100)
Survivin, specific nuclear form	7	1.5 (0-20)
IAP-2[1]	32	90 (30-100)
IAP-1	32	95 (40-100)
X-IAP	22	50 (0-100)
Smac/DIABLO	11	5 (0-90)
Apoptotic index (CK18-caspase cleavage product)	-	0.45 (0-5.8)
Proliferation index (Ki-67)	-	10 (0-50)

[1]Cytoplasmic/nuclear subcellular distribution.

MOLECULAR THERAPEUTIC TARGETS

Apoptotic cell death is the main mode by which chemical and physical anticancer agents kill tumor cells. Dysregulation of the apoptotic pathways may play a role in the relative chemo-resistance of DMPM, as already demonstrated for pleural mesothelioma[47]. Better understanding of the biological mechanisms underlining the apoptosis-resistant phenotype could result in novel targeted therapeutic strategies. For this purpose, the expression of survivin and other IAP family members, including IAP-1, IAP-2, and X-IAP, were analyzed by immunohistochemistry in surgical specimens of 32 patients with DMPM uniformly treated by CRS and HIPEC at the Milan NCI[48]. The staining characteristics of the pro-apoptotic protein Smac/DIABLO, of the Ki-67 antigen associated with cell proliferation and of the caspase-cleaved cytokeratin 18 associated with apoptosis were also studied.

The results of the immunostaining studies are shown in Table 3. Survivin was expressed in the cytoplasm in 19 DMPM cases (59%), at the nuclear level in 2 DMPM cases (6%) and at both cytoplasmic and nuclear levels in 5 DMPM cases (16%). In the remaining 6 cases, no survivin immunoreactivity was seen. IAP-2 and IAP-1 were expressed in 100% of cases. X-IAP was expressed in 22/32 cases (68.7%) and Smac/DIABLO in 11/32 cases (34.4%). The CK18-caspase cleavage product staining was positive in a median of 0.45% cells and Ki-67 was positive in a median of 10% cells. Caspases are the executioners of apoptosis in both intrinsic and extrinsic pathways[49]. The activated caspases are subject to inhibition by IAPs through direct binding[50]. This inhibitory effect can be abrogated by Smac/DIABLO, a pro-apototic factor released

from mitochondria that reactivates initiator and effector caspases, by binding to IAPs and relieving IAP-mediated inhibition[51].

All 4 IAP family members were simultaneously over-expressed in 16/32 cases, while a lack of expression was consistently found in normal peritoneum, suggesting that these anti-apoptotic proteins are heavily dysregulated in DMPM. Furthermore, an inverse association was found between Smac/DIABLO expression and IAPs co-expression.

Such results provide important insights in DMPM biology. Although cell proliferative index (KI-67) was mostly low, an antigen associated to apoptosis, such as CK-18 caspase cleavage product, was poorly expressed. Furthermore, a concurrent over-expression of apoptosis inhibitor factors and poor expression of pro-apoptotic factors was seen in the majority of cases. This pattern suggests that resistance to programmed cell death may contribute to the chemo-insensitivity of DMPM.

In recent years, considerable efforts have been made to develop strategies for modulating apoptosis in cancer[52]. In this context, approaches to counteract survivin aim to inhibit tumor growth and enhance tumor cell responses to apoptosis-inducing agents[53]. An RNA-interference-based strategy was used to down-regulate survivin expression in a human peritoneal mesothelioma cell line (STO) recently established in our laboratory[54]. Cells were transfected with survivin small interfering RNA (siRNA) or control siRNA. The effects of siRNA-mediated survivin down-regulation was evaluated by enhanced chemoluminescence Western blotting, flow cytometry, fluorescence microscopy and at a molecular level.

Western blotting experiments carried out in cells transfected with survivin-specific siRNA showed a significant reduction of survivin, as compared to cells transfected with control siRNA (Figure 2). Silencing of the survivin gene resulted in a significant and time-dependent decline in cell proliferation.

In cells transfected with survivin siRNA, an apoptotic sub-$G_{0/1}$ peak was observed by flow cytometry and the presence of cells with an apoptotic nuclear morphology was assessed by fluorescence microscopy. At a molecular level, a significantly increased catalytic activity of caspase-9 was seen.

A number of *in vitro* and *in vivo* studies indicated that survivin down-regulation was able to sensitize human tumor cells of different histologic origin to conventional chemotherapeutic drugs with distinct mechanisms of action as well as to ionizing radiation[53,55]. To test whether survivin plays a role in the *in vitro* sensitivity of DMPM cells to anticancer drugs, we examined the effect of survivin down-regulation on the apoptotic response to cisplatin and doxorubicin. Exposure to cisplatin and doxorubicin induced a dose-dependent increase in the percentage of apoptotic cells, which was significantly ($P < 0.01$ for cisplatin and $P < 0.05$ for doxorubicin) higher in cells exposed to the survivin siRNA than in those transfected with control siRNA or treated with oligofectamine. A dose-dependent increase in caspase-9 catalytic activity was also observed.

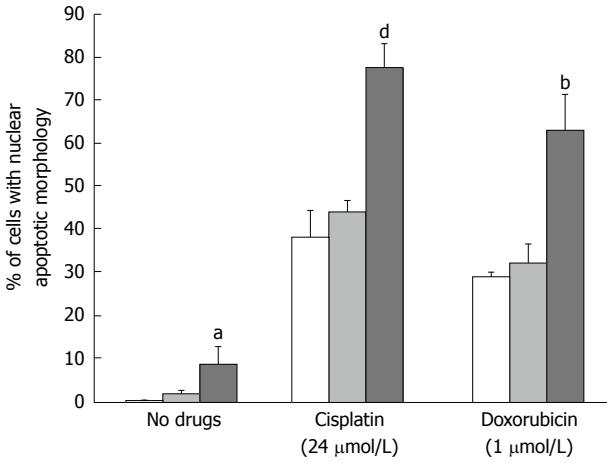

Figure 3 Effects of siRNA-mediated survivin down-regulation on the apoptotic response of STO cells to cisplatin and doxorubicin. The percentage of cells with an apoptotic morphology with respect to the overall population as assessed by fluorescence microscopy in STO cells exposed to oligofectamine alone (empty column) and transfected with control siRNA (gray column) or survivin siRNA (black column) in the absence or presence of different cisplatin or doxorubicin concentrations. Data represent mean ± SD of 3 independent experiments. $^{a}P < 0.05$; $^{b}P < 0.01$; $^{d}P < 0.001$; Student's *t* test.

These findings demonstrate that the level of survivin expression influences the *in vitro* response of DMPM cells to cisplatin and doxorubicin. This has potential clinical implications since it could provide a rational basis for the design of combined therapies, including survivin inhibitors, to improve the responsiveness of DMPM to chemotherapy. However, considering the presence of other anti-apoptotic factors, it is likely that approaches based on the simultaneous targeting of different cytoprotective factors could obtain enhancement of DMPM cell chemo-sensitivity (Figure 3).

Little is known about receptor tyrosine kinase (RTK) activation in malignant peritoneal mesotheliomas[33,56]. We performed *EGFR*, *PDGFRA* and *PDGFRB* analyses to ascertain if deregulation of RTK could offer useful alternative therapeutic targets in this tumor[57].

EGFR, *PDGFRA* and *PDGFRB* expression and phosphorylation were immunohistochemically and biochemically analysed in 15 DMPM cases. The tyrosine kinase domain (exons 18-21) of the *EGFR* gene were automatically sequenced, as well as the extracellular (exon 10) and juxtamembrane regions (exon 12) and the tyrosine kinase domain (exons 14 and 18) of *PDGFRA* and *PDGFRB*. The cognate ligand expression was investigated by real time PCR. Additionally, we explored the status of RTK downstream pathways through mutational and biochemical analysis of the *PI3KCA* gene (exons 9 and 20)/PTEN/AKT, and ERK, along with mTOR and its effector S6.

Immunohistochemical and immunoprecipitation/Western blotting analyses showed *EGFR*, *PDGFRA* and *PDGFRB* expression and activation in most of the cases. In particular, *EGFR* and *PDGFRA* were more frequently phosphorylated than *PDGFRB*. Autocrine loop activation of these receptors was suggested in all

cases by the expression of the related cognate ligands *TGF-a*, *PDGFA* and *PDGFB*, in absence of receptor gain of function mutations. No *PI3KCA* mutations were found, while all the MPMs showed expression of PTEN and expression/activation of AKT, ERK, as well as of mTOR and S6. These data suggest that *EGFR*, *PDGFRA* and *PDGFRB* seem to be promising molecular targets for tailored treatments in MPM. Furthermore, strong activation of downstream signalling points out a role of mTOR inhibitors or analogous in MPM treatment.

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TOPIC HIGHLIGHT

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Multidisciplinary therapy for treatment of patients with peritoneal carcinomatosis from gastric cancer

Yutaka Yonemura, Ayman Elnemr, Yoshio Endou, Mitsumasa Hirano, Akiyoshi Mizumoto, Nobuyuki Takao, Masumi Ichinose, Masahiro Miura, Yan Li

Yutaka Yonemura, Ayman Elnemr, NPO Organization to Support Peritoneal Dissemination Treatment, Kishiwada, Osaka 596-0032, Japan
Yoshio Endou, Department of Experimental Therapeutics, Cancer Research Institute, Kanazawa University, Kanazawa 920-8640, Japan
Mitsumasa Hirano, Akiyoshi Mizumoto, Nobuyuki Takao, Masumi Ichinose, Department of Surgery, Kusatsu General Hospital, Shiga 525-8585, Japan
Masahiro Miura, Department of Anatomy, School of Medicine, Ooita University, Ooita 879-5593, Japan
Yan Li, Department of Oncology, Zhongnan Hospital of Wuhan University, No. 169, Donghu Road, Wuchang District, Wuhan 430071, Hubei Province, China
Author contributions: All the authors contribute to this work; Yonemura Y wrote this work.
Correspondence to: Yutaka Yonemura, MD, PhD, NPO Organization to Support Peritoneal Dissemination Treatment, 1-26, Haruki-Moto-Machi, Kishiwada, Osaka 596-0032, Japan. y.yonemura@coda.ocn.ne.jp
Telephone: +81-72-4332131 Fax: +81-72-4332131
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Abstract

There is no standard treatment for peritoneal carcinomatosis (PC) from gastric cancer. A novel multidisciplinary treatment combining bidirectional chemotherapy [neoadjuvant intraperitoneal-systemic chemotherapy protocol (NIPS)], peritonectomy, hyperthermic intraperitoneal chemoperfusion (HIPEC) and early postoperative intraperitoneal chemotherapy has been developed. In this article, we assess the indications, safety and efficacy of this treatment, review the relevant studies and introduce our experiences. The aims of NIPS are stage reduction, the eradication of peritoneal free cancer cells, and an increased incidence of complete cytoreduction (CC-0) for PC. A complete response after NIPS was obtained in 15 (50%) out of 30 patients with PC. Thus, a significantly high incidence of CC-0 can be obtained in patients with a peritoneal cancer index (PCI) ⩽ 6. Using a multivariate analysis to examine the survival benefit, CC-0 and NIPS are identified as significant indicators of a good outcome. However, the high morbidity and mortality rates associated with peritonectomy and perioperative chemotherapy make stringent patient selection important. The best indications for multidisciplinary therapy are localized PC (PCI ⩽ 6) from resectable gastric cancer that can be completely removed during a peritonectomy. NIPS and complete cytoreduction are essential treatment modalities for improving the survival of patients with PC from gastric cancer.

Key words: Gastric cancer; Peritoneal carcinomatosis; Chemotherapy

Peer reviewer: Ugur Coskun, MD, Associate Professor, Department of Medical Oncology, Gazi University Medical School, Besevler, Ankara 06500, Turkey

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INTRODUCTION

Peritoneal carcinomatosis (PC) is a stage Ⅳ factor of gastric cancer and has been generally associated with a grim prognosis[1,2]. No standard treatment for PC has been proposed and surgery or chemotherapy alone has no beneficial effect on survival.

Sugarbaker and Yonemura propose a new multimodal treatment called cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC)[3], which utilizes surgery to reduce the visible tumor burden and HIPEC to eradicate peritoneal micrometastasis and peritoneal free cancer cells (PFCCs). Survival analyses after CRS plus HIPEC have shown that complete cytoreduction is associated with an improvement in survival[3].

Neoadjuvant chemotherapy has been proposed as a method of reducing tumor burden before surgery, resulting in a higher incidence of complete cytoreduction[4]. A new bidirectional chemotherapy regimen [neoadjuvant intraperitoneal-systemic chemotherapy protocol (NIPS)] has been developed to reduce the volume and peritoneal cancer index of PC[4]. NIPS attacks PC from both sides of the peritoneum: from the peritoneal cavity and from the subperitoneal blood vessels. Accordingly, NIPS is known as bidirectional chemotherapy.

Early postoperative intraperitoneal chemotherapy (EPIC) can eradicate residual intraperitoneal cancer cells before fibrin can accumulate around residual cancer cells on the peritoneal surface.

In this review, the latest results of multidisciplinary treatment consisting of bidirectional chemotherapy (NIPS), CRS (peritonectomy), HIPEC and EPIC for patients with established PC from gastric cancer are considered.

MULTIDISCIPLINARY THERAPY FOR THE TREATMENT OF PC FROM GASTRIC CANCER

The median survival period of patients with PC from gastric cancer is reportedly 7 mo after diagnosis and best-supportive care[2]. There are many reports examining the use of systemic chemotherapy but few have focused on PC from gastric cancer. Intravenous 5FU infusion, alone or in combination with other anticancer drugs (FAM[5], FAMTX[6]), has been used in patients with advanced gastric cancer. Recently, Ajani[7] reported that DCF therapy (a combination chemotherapy using docetaxel, CDDP and 5FU) exhibited a significantly better survival outcome than CF (CDDP + 5FU) therapy. However, these regimens have little effect on the survival of patients with PC. To overcome the limitations of systemic chemotherapy, a novel combination chemotherapy regimen comprised of CRS and bidirectional chemotherapy (NIPS and EPIC) has been proposed[8-10].

Recently, a new drug named S-1 has been used for the treatment of PC from gastric cancer in Japan. Positive results for response and for the improvement of survival have been reported after the oral administration of S-1. Accordingly, S-1 or S-1 in combination with other drugs, such as cisplatinum, paclitaxel, docetaxel or irinotecan, has become the standard regimen for the treatment of PC from gastric cancer.

Recently, new multidisciplinary therapies combining CRS and perioperative chemotherapy have been reported[4,10]. These therapies consist of NIPS, CRS, HIPEC and EPIC (Figure 1).

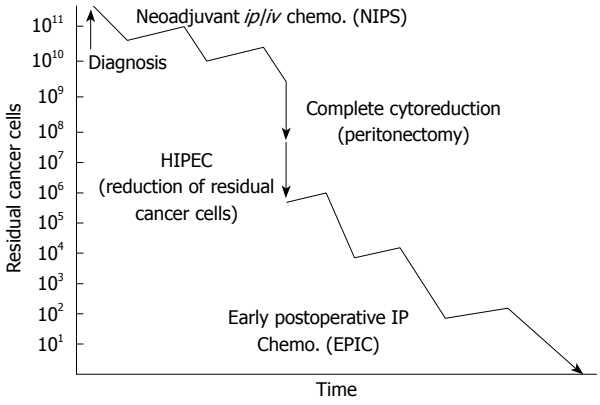

Figure 1 Treatment strategy for PC from gastric cancer. PC: Peritoneal carcinomatosis; NIPS: Neoadjuvant intraperitoneal-systemic chemotherapy protocol; HIPEC: Hyperthermic intraperitoneal chemoperfusion; EPIC: Early postoperative intraperitoneal chemotherapy.

Patients who have been diagnosed with PC based on the results of an exploratory laparotomy, diagnostic laparoscopy or computed tomography are treated with NIPS followed by CRS to enable complete cytoreduction. Immediately after CRS, HIPEC is performed for one hour. After surgery, EPIC is performed on postoperative days 1 to 5[11], and systemic chemotherapy is performed on postoperative days 30-40.

NEOADJUVANT BIDIRECTIONAL CHEMOTHERAPY (NIPS)

The aims of neoadjuvant chemotherapy (NAC) are stage reduction, eradication of micrometastasis outside the surgical field, and the improvement of resectability. Usually, systemic chemotherapy is used for NAC. In the late 1990s, TS-1, irinotecan, taxanes and docetaxel were introduced and the response rate after monotherapy with these drugs was around 20%. Combination chemotherapy with S-1 and CDDP produced outstanding results, with a response rate of 74%[12]. Yabusaki *et al*[13] reported the results of NAC with S-1 and CDDP in 37 advanced gastric cancer patients scheduled to undergo non-curative resection. After 2 courses of treatment, the overall response rate was 68%, but the response rate for patients with peritoneal dissemination was only 14% (2/14). S-1 plus CPT-11 and CPT-11 plus CDDP produced a high response rate of 42% and a long period of progression-free survival, but treatment failure as a result of toxicity was also observed[14].

Ajani[7] reported an excellent response rate (55.7%) to systemic DCF therapy combined with docetaxel (75 mg/m^2 on day 1, q 3 wk), CDDP (75 mg/m^2 on day 1, q 3 wk), and 5FU (750 mg/m^2 on days 1 to 5, q 3 wk) However, the effects on PC were not described.

In addition, the one-month mortality rate and the incidence of grade 3 or 4 toxicity after DCF therapy were 8% and 60% respectively. Accordingly, a high incidence of postoperative complications can be expected during the postoperative period after DCF therapy.

Table 1 Area under the curve ratios of intraperitoneal exposure to systemic agents

Drugs	Area under the curve ratio
5-Fluorouracil	250
Carboplatin	10
Cisplatin	7.8
Docetaxel	552
Doxorubicin	230
Etoposide	65
Gemcitabin	500
Irinotecan	N/A
Melphalan	93
Mitomycin C	23.5
Mitoxantrone	115-255
Oxaliplatin	16
Paclitaxel	1000
Pemetrexed	40.8

These results indicate that systemic chemotherapies have minimal effects on PC[15]. In other words, the peritoneal cavity acts as a sanctuary against systemic chemotherapy probably because of the existence of a blood-peritoneal barrier consisting of stromal tissue between mesothelial cells and submesothelial blood capillaries[8]. This barrier accounts for a total thickness of 90 μm[16]. Accordingly, only a small amount of systemic drugs are capable of penetrating this barrier and passing into the peritoneal cavity so a higher percentage of the administered drugs instead moves to the bone marrow and vital organs other than the peritoneum, resulting in the development of adverse effects.

In contrast, IP chemotherapy offers potential therapeutic advantages over systemic chemotherapy by generating high local concentrations of chemotherapeutic drugs in the peritoneal cavity[9,17]. This concentration difference enables the exposure of small nodules of PC before CRS and lowers the systemic toxicity. This advantage of IP chemotherapy can be expressed by the area under the curve (AUC) ratios of intraperitoneal versus plasma exposure.

Table 1 shows the AUC IP/systemic for various drugs[15]. Relatively high AUC/systemic ratios were obtained after the IP administration of paclitaxel, docetaxel, gemcitabine, 5-fluorouracil and doxorubicin. These drugs may be good candidates for IP chemotherapy. Other important factors in the selection of drugs for IP chemotherapy are a high penetration activity into the PC nodules and chemosensitivity. Each drug has its own penetration depth into the peritoneal surface and the effective diffusion distance into tissues reportedly ranges from 100 to 1000 μm[17,18]. Adriamycin can penetrate only 4-6 cell layers of experimental tumors[18], but cisplatin and carboplatin were confirmed to penetrate 1 to 2 mm from the surface of PC nodules[17]. The penetration distance depends on the specific drug and type of tumor. Thus, any superiority of intraperitoneal chemotherapy over intravenous delivery is limited to those PC patients with very small tumor volumes of less than 2 mm.

An *in vitro* chemosensitivity test using the collagen-gel method in human gastric cancer tissues[4] showed that the tissues were highly sensitive to 5-FU, carboplatin, cisplatin and docetaxel. In an experimental PC model using a highly metastatic cell line derived from human gastric cancer in the peritoneal cavity, docetaxel, 5-FU, carboplatin and TS-1 plus cisplatin were highly effective for improving the survival of nude mice[19] and the IP administration of these drugs is expected to become standard therapy for gastric cancer patients[10,17,20,21].

From these experimental results, a new bidirectional chemotherapy combined with the oral administration of S-1 and IP CDDP and docetaxel has been developed. By simultaneously administering intravenous and intraperitoneal chemotherapy, a bidirectional diffusion gradient can create a wider treatment area than single treatment. As shown in Figure 2, a peritoneal port system (Hickman Subcutaneous port; BARD, Salt Lake City, USA) was introduced into the abdominal cavity under local anesthesia, and the tip of the system was placed on the cul-de-sac of Douglas. Then, a peritoneal wash cytology was performed after 500 mL of physiological saline was injected into the peritoneal cavity. To improve the accuracy of the cytology, an immunohistochemical examination using monoclonal antibodies for anti-human carcinoembryonic antigen (TAKARA Bio INC., Tokyo, Japan) and anti-human epithelial antigen (DAKO, Copenhagen, Denmark) was performed. A peritoneal wash cytological examination was performed before and after NIPS.

Patients were treated with 60 mg/m^2 of oral S-1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) for 21 d, followed by a one week rest. On days 1, 8, and 15 after the start of oral S-1 administration, 30 mg/m^2 of Taxotere and 30 mg/m^2 of cisplatinum with 500 mL of saline were introduced through the port. This regimen was repeated after a one week rest[10].

Bidirectional chemotherapy is used before surgery to reduce the peritoneal surface involved by PC and to eradicate peritoneal free cancer cells (PFCCs). Accordingly, it may facilitate a complete cytoreduction after chemotherapy. This approach was given the acronym Neoadjuvant Intra Peritoneal and Systemic chemotherapy (NIPS)[22]. Yonemura *et al*[10] reported the outcomes of 79 gastric cancer patients with PC who were treated with NIPS: no chemotherapy-related deaths after NIPS occurred in this series. Furthermore, grade 4 bone marrow toxicity developed in only 1 (1.3%) of the 79 patients. Renal dysfunction occurred in 3 patients (3.8%) but these patients recovered fully. Accordingly, the new bidirectional chemotherapy regimen is considered to be a safe method[10].

A distinctive complication of this treatment is subcutaneous infection around the periportal space, which was observed in 3 patients (3.8%). When infection is detected, the port should be removed under local anesthesia. Peritoneal lavage cytology from a port system detected PFCCs in 65 (82.2%) of 79 patients before NIPS; these positive cytology results became negative in 41 patients (63.0%) after NIPS[10]. Positive cytology results obtained before NIPS became negative in 4 (40.0%) of 10 patients after one treatment cycle. In contrast, 37 (67.2%) of 55 patients with positive cytology results before NIPS

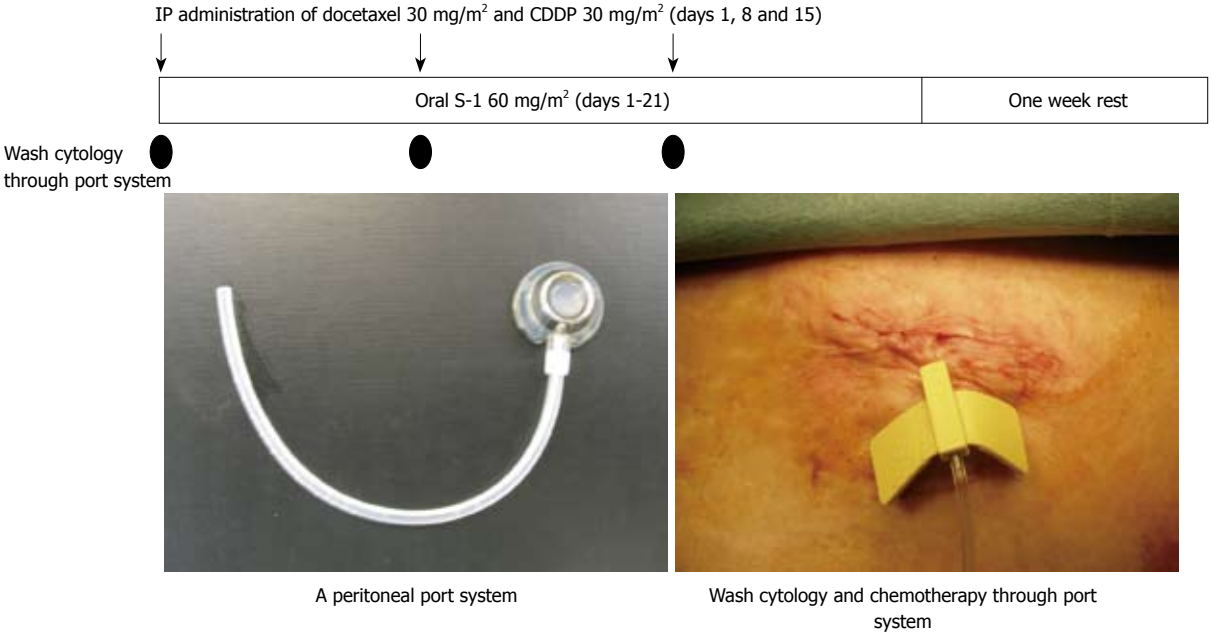

Figure 2 Bidirectional chemotherapy for peritoneal carcinomatosis from gastric cancer.

Table 2 Operation methods in 30 primary gastric cancer patients with PC after NIPS

Extent of gastrectomy
Total gastrectomy: 29
Distal gastrectomy: 1
LN dissection
D2 dissection: 29
D1 dissection: 1
Peritonectomy procedures
Diaphragm copula: right side 1, both side 2
Colon resection : 9
Hysterectomy + BSO: 9
Douglasectomy: 7
Small bowel/mesentery resection: 4
Falciform ligament resection: 30
Morrison Pouch resection: 29
Omentectomy: 30
Anterior leaf of transverse colon: 29
Splenectomy: 28
Completeness of cytoreduction
Complete cytoreduction: 24 (80.0%)

PC: Peritoneal carcinomatosis; NIPS: Neoadjuvant intraperitoneal-systemic chemotherapy protocol.

obtained negative cytology results after two or more cycles of NIPS. Accordingly, NIPS is a very powerful treatment modality for eradicating PFCCs and two cycles of NIPS is recommended to achieve a negative cytology status.

NIPS reportedly adds to the morbidity and mortality of further surgical treatment[23,24]. Table 2 shows the surgical methods and the rate of complete cytoreduction in our experience with 30 primary gastric cancer patients who had a gastrectomy plus peritonectomy after NIPS[10]. A total gastrectomy and D2 lymphadenectomy were performed in 29 patients and some parts of the peritoneum were removed in combination with the gastrectomy. As a result, a complete cytoreduction was achieved in 24 patients (80%). No postoperative mortalities occurred but morbidities occurred in 5 (16.7%) of the 30 patients, a morbidity rate similar to that after a gastrectomy with an aggressive lymphadenectomy[25].

After systemic neoadjuvant chemotherapy, a complete PC response is very rare. Inokuchi *et al*[26] reported that the response rate of PC after S-1 plus irinotecan was 69% (9/13), but no CR was experienced for PC. Baba also reported the limited effects of systemic S-1+CDDP on PC from gastric cancer[27]. Figure 3A and B shows the macroscopic and histologic changes in the primary tumor after NIPS. Almost all the cancer cells have disappeared and only mucin remains in the primary tumor. A histologic change similar to that seen in Figure 3B corresponds to a histological grade of 3, according to the general rules for gastric cancer treatment in Japan[28]. A histologic grade of 1 means the degeneration of cancer is detected in less than two third of the tumor tissue, while a grade of 3 means the complete disappearance of the cancer cells. Histologic effects on primary tumors were found in 25 of the 30 tumors, and Grade 1, 2 and 3 evaluations were made in 10 cases (33.3%), 14 (46.7%) and 1 (3.3%) respectively. In contrast, the complete histologic disappearance of PC was observed in 15 (50%) of 30 patients (Figure 4A-D). Stage migration from stage 4 to stage 1, 2 or 3 was experienced in 10 patients (33.3%). Accordingly, NIPS is a powerful strategy for eradicating PFCCs and macroscopic PC, resulting in stage migration[29].

CRS USING PERITONECTOMY PROCEDURES

The current state-of-the-art treatment for colorectal peritoneal dissemination is a comprehensive management using CRS and HIPEC. Patients with a low tumor volume, well/moderately differentiated tumors and complete

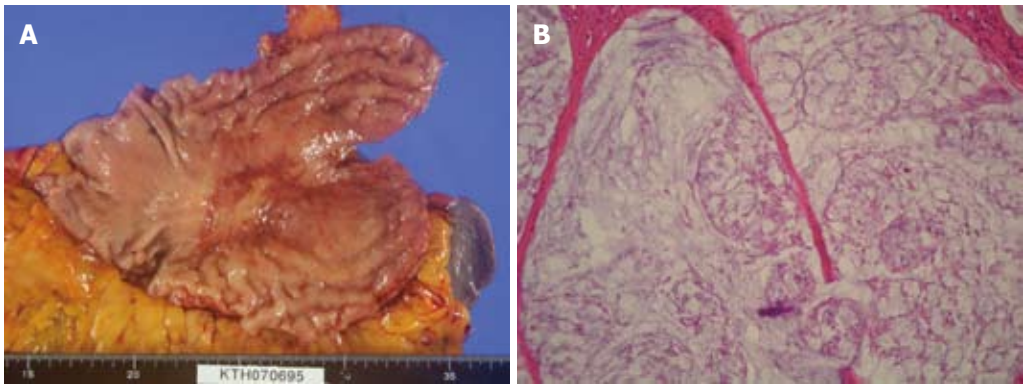

Figure 3 A 34-year old female patient with PC from type 4 gastric cancer treated with NIPS. A: Macroscopic finding of resected stomach of patients treated with NIPS; B: Histologic finding of resected stomach of patient treated with NIPS. Almost all cancer cells disappear and mucin alone was depicted in the primary tumor (histological grade 3).

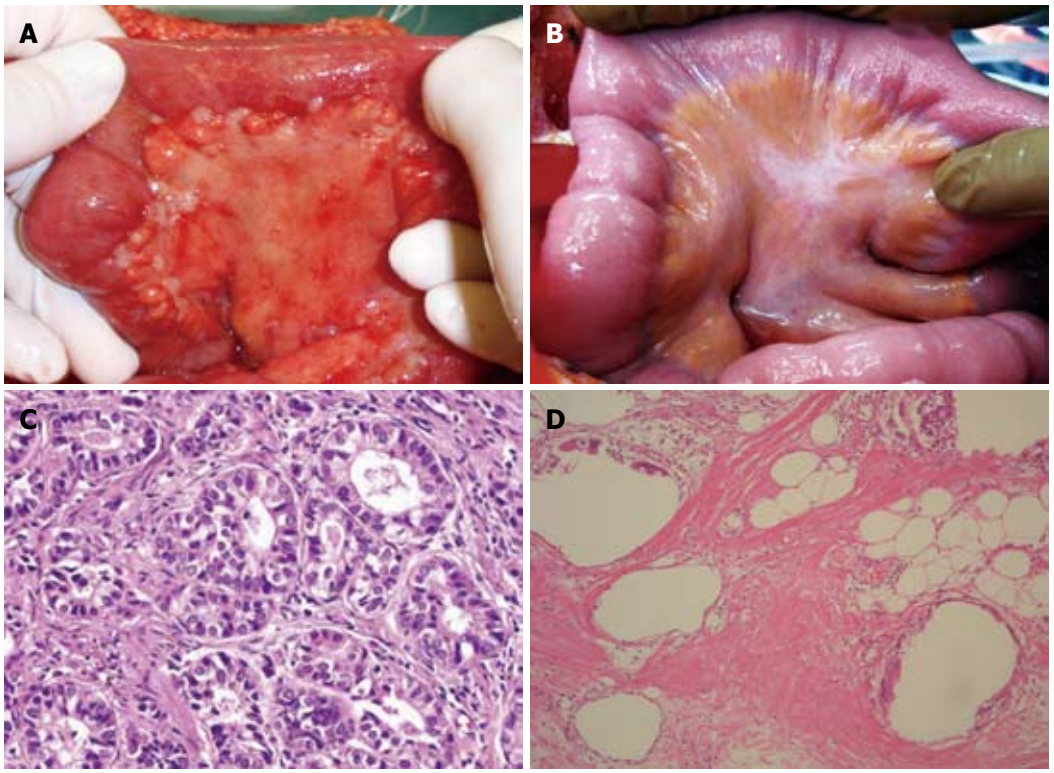

Figure 4 A 48-year old male patient with PC from gastric cancer treated with NIPS. A: Macroscopic finding of PC on bowel mesentery; B: After 2 courses of NIPS, PC nodules shows fibrotic changes; C: Histologic findings of PC nodule obtained at the first operation of Figure 4A; D: Complete degeneration of cancer cells in PC nodule obtained at second look operation after NIPS.

cytoreduction may potentially benefit from combined treatment[30]. In gastric cancer patients with PC, no survival benefit has been reported by cytoreduction alone. In contrast, CRS with peritonectomy plus HIPEC confers a prolonged survival period[10]. Complete cytoreduction is an essential factor for a good outcome and NIPS plus peritonectomy may improve the incidence of complete cytoreduction[29,31]. Glehen *et al*[32] reported that CRS and HIPEC might have a survival benefit in highly selected patients (good general condition, resectable primary gastric cancer and PC).

However, NIPS might increase the risk of a peritonectomy procedure plus a gastrectomy combined with a lymphadenectomy. Glehen reported a mean operation time of 5.2 h (range 1.5-9.5 h), a 30-d mortality rate of 4% (2/49), and a major complication rate of 27% (13/49)[32]. In our consecutive series of 96 gastric cancer patients with PC, two hospital deaths (2%) occurred in patients who died of MOF from pancreatic fistula and sepsis. Postoperative major complications occurred in 30 (32%) patients (Table 3)[10]. A second operation was necessary in 4 patients who had complications from insufficiency of esophagojejunal anastomosis, bleeding, and ileal and colonic fistula. Glehen reported a higher complication rate of 47% in patients who underwent extensive CRS (gastrectomy combined with the removal of more

Table 3 Postoperative complications after 96 peritonectomy for PC from gastric cancer

Medical complication	
Pulmonary complications	5 (5%)
Surgical complication	
Anastomotic leakage	11 (10%)
Fistula from small bowel	4 (4%)
Abdominal abscess	4 (4%)
Bleeding	3 (3%)
Pancreatic fistula	2 (2%)
Reoperation	4 (4%)
Bleeding	1
Drainage of abscess	
From leakage	1
From bowel fistula	2

than 2 peritoneal zones)[32]. The magnitude of surgery, the number of resected organs, the number of anastomoses and the operation time are considered to have contributed to the significantly higher complication rate.

To avoid futile aggressive treatments, the preoperative stringent selection of patients must be emphasized. Surgeons should have a large amount of surgical experience with gastrointestinal and genitourinary diseases and an extensive knowledge of organ anatomy and physiology. Surgeons must also be able to judge the balance between the postoperative risk associated with the magnitude of the peritonectomy and the survival benefit and quality of life.

Yan *et al*[33] reported the existence of a learning curve with this procedure and recommended the accumulation of experience to achieve an acceptable morbidity rate. They proposed that at least 70 peritonectomy procedures are needed to obtain a reliable level of surgical proficiency and postoperative care. Surgeons who want to perform this procedure must have a surgical team that includes anesthesiologists, nurses, pathologists, urologists, gynecologists and other experienced surgeons.

QUANTITATIVE ESTIMATION AND PREOPERATIVE DIAGNOSIS OF PC

For the objective evaluation of the distribution and volume of PC, a quantitative staging system is needed. In the Japanese Rules of Gastric Cancer, PC is classified into five categories[28]: P0/Cy0, P0/Cy1, P1, P2 and P3. P0/Cy0 means no macroscopic disease and a negative peritoneal wash cytology; P0/Cy1 means no macroscopic PC but a positive peritoneal wash cytology; P1 means PC in the upper abdomen above the transverse colon; P2 means several countable PC in the peritoneal cavity; and P3 means numerous PC in the peritoneal cavity. The size of the PC is not taken into consideration in the Japanese staging system. The Japanese staging system itself has been shown to be an important prognostic factor. Significant survival differences in the survival rates were observed between P1 *vs* P2, P1 *vs* P3, and P2 *vs* P3 group (Figure 5).

A unique point of the Japanese classification is the performance of a cytological examination using peritoneal wash fluid, even in patients who are scheduled to undergo a potentially curative resection. The peritoneal wash cytology is usually negative when the macroscopic diameter of the serosal invasion of the primary tumor is smaller than 2 cm (Figure 6). Furthermore, for serosal involvement with a diameter larger than 5 cm, the peritoneal wash cytology was reportedly positive in 66% (101/153) of the patients[34].

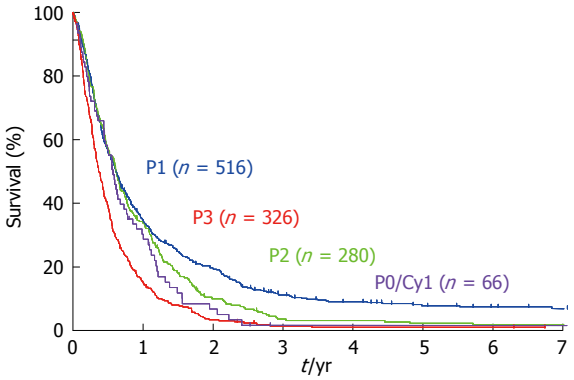

Figure 5 Survival curves of patients with PC, according to the Japanese classification. P1 *vs* P2: $P < 0.025$, $\chi^2 = 4.979$; P1 *vs* P3: $P < 0.001$, $\chi^2 = 61.13$; P0/Cy1 *vs* P2, P3: Not significant.

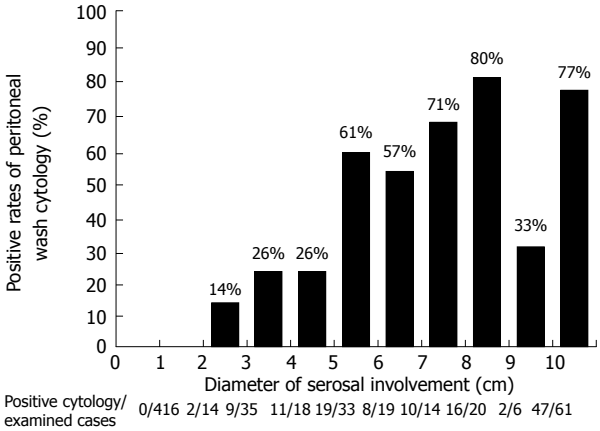

Figure 6 Positive rates of peritoneal wash cytology according to the diameter of serosal involvement of primary tumor. Intraoperative cytological examination of the peritoneal wash solution using 200 mL of saline in 637 patients who had no macroscopic PC.

PFCCs have a high proliferative activity (Figure 7) because the Ki-67 labeling rate of PFCCs is high (median value, 60%)[34,35]. The median survival time of patients with a positive cytology result is 6 mo, and the survival curve of patients with P0/Cy1 is not statistically significant, compared with that of patients with P1, 2, or 3 statuses (Figure 5)[35,36]. Accordingly, P0/Cy1 patients are regarded as having stage Ⅳ disease. A peritoneal wash cytology is recommended in gastric cancer patients scheduled to undergo curative resection.

Gilly proposed a new staging system that takes into account the size of the peritoneal nodules and their distribution (localized or diffuse) (Table 4). This staging system has also been confirmed to be an important prognostic indicator[32]. Since the median survival of patients with stage 1 or 2 is significantly better than those

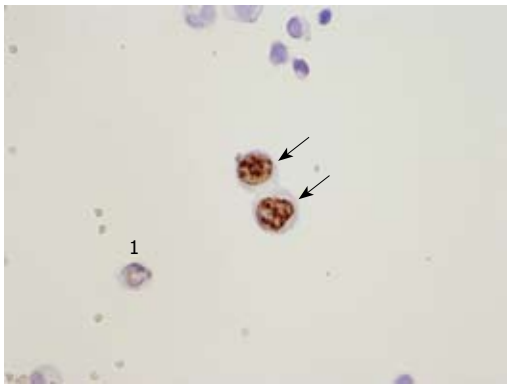

Figure 7 Ki-67 expression in PFCCs (immunocytochemical staining using MIB-1). [1]Cancer cell without expression of Ki-67. Arrows indicate Ki-67 positive PFCCs with proliferative activity.

Table 4 Gilly staging system

Stage	Peritoneal carcinomatosis description
Stage 0	No macroscopic disease
Stage 1	PC less than 5 mm in diameter localized in one part of abdomen
Stage 2	PC less than 5 mm Diffuse in the whole abdomen
Stage 3	PC 5 mm to 2 cm in diameter
Stage 4	Large PC more than 2 cm

with stage 3 or 4 after CRS and HIPEC, patients with stage 1 or 2 could be candidates for CRS and HIPEC.

Sugarbaker reported the use of the peritoneal cancer index (PCI)[37]. This staging system accounts for both cancer distribution and size of peritoneal nodules (Figure 8). The abdominal cavity is subdivided into 13 regions. Furthermore, the accurate sizes of the lesions in each region are recorded by direct visual inspection intraoperatively. The macroscopic PC nodules in each zone are meticulously observed during surgery and scored from 0 to 3. Score 0 means that no nodules seen; score 1 has nodules with a maximum visible diameter of up to 0.5 cm; score 2 a diameter of greater than 0.5 cm and up to 5 cm; and score 3 refers to nodules with a diameter of 5 cm or greater. Peritoneal nodules are scored as lesion sizes 0 through 3 (LS 0 to LS 3) (Figure 8). This method quantifies the extent of PC in the peritoneal cavity, which can be summated as a numerical score (from 0 to 39).

Sugarbaker proposed a means of assessing the completeness of cytoreduction (CC), classified into four categories. CC-0 indicates complete cytoreduction with no residual macroscopic nodule; CC-1 no macroscopic tumor but a positive histological margin or suspicious residual nodules less than 5 mm in diameter; CC-2 apparent macroscopic residual tumors greater than 5 mm but up to 5 cm in diameter; and CC-3 residual PC greater than 5 cm in diameter.

In patients with gastric cancer who have received a CC-0 or CC-1 peritonectomy, involvement was not found on the anterior abdominal wall and liver capsule but was observed in other zones in 10 cases (2.7% to 35%). In contrast, all the zones were involved in the CC-2 or CC-3 group. A higher incidence of diffuse involvement on the serosal surface or mesentery of the small and large bowel was seen in the CC-2 or CC-3 group. In patients with colorectal cancer, Koh *et al*[38] reported a predilection for the right side, with spreading to the right upper and flank regions being approximately twice as common as to the left regions. The right upper and flank regions correspond to the right diaphragmatic copula and the right paracolic gutter of the ascending colon. Furthermore, they reported that the small bowel segment was the least commonly affected area, with the exception of the distal ileum. During laparoscopic examination and exploratory laparotomy, surgeons should meticulously observe and palpate these 13 zones[36].

The complete cytoreduction of patients with PCI $\leqslant$ 6 and PCI $\geqslant$ 7 has been reportedly performed in 86% (49/57) and 39% (14/41) of patients respectively (Figure 9). These percentages were significantly different ($P < 0.05$). Complete cytoreduction was successfully performed in only 7% (2/27) of patients with a PCI greater than 13.

The PCI score is believed to be an independent prognostic factor and a PCI score capable of serving as a threshold for favorable versus poor prognosis has been reported. In colorectal cancer, the survival results are significantly better when the PCI was lower than 16[37,39]. In a series of patients with colorectal cancer, Sugarbaker reported a 5-year survival rate of 50% when the PCI was less than 10, a rate of 20% for an index of 11-20, and a rate of 0% for an index > 20[40]. Berthet *et al*[41] reported that the PCI score predicted a benefit to the visceral organs from the treatment of sarcomatosis. The PCI score system developed by Sugarbaker is now used worldwide for the assessment of PC from various tumor types.

As shown in Figure 10, the survival of gastric cancer patients with a PCI score $\leqslant$ 6 was significantly better than those with a PCI score $\geqslant$ 7. Gastric cancer is believed to have a more aggressive biological behavior than colorectal cancer. These results suggest that carcinomatosis from gastric cancer with a PCI score greater than 7 should be treated with palliative intent without peritonectomy.

For the preoperative diagnosis of PC, computed tomography (CT), magnetic resonance imaging (MRI), PET-CT and laparoscopy are performed as part of the stringent patient selection required for peritonectomy[42]. The availability and lower incidence of movement artifacts make multi-sliced CT the most widely used imaging tool for the detection of PC. High-speed spiral CT for the detection of PC from gastric cancer has an accuracy of 78%, a sensitivity of 39%, a specificity of 94%, a positive predictive value of 72% and a non-predictive value of 79%[42].

Koh *et al*[38] reported the value of preoperative CT in estimating PC in patients with colorectal carcinomatosis. CT portrayed the lesion size accurately in 60% of the cases, underestimated the size in 33% of the cases, and overestimated the size in 7% of the cases. The detection rates depended on the peritoneal zone and lesion size. The detection rates for PC are relatively high in the epigastrium, right upper area, and pelvis with detection

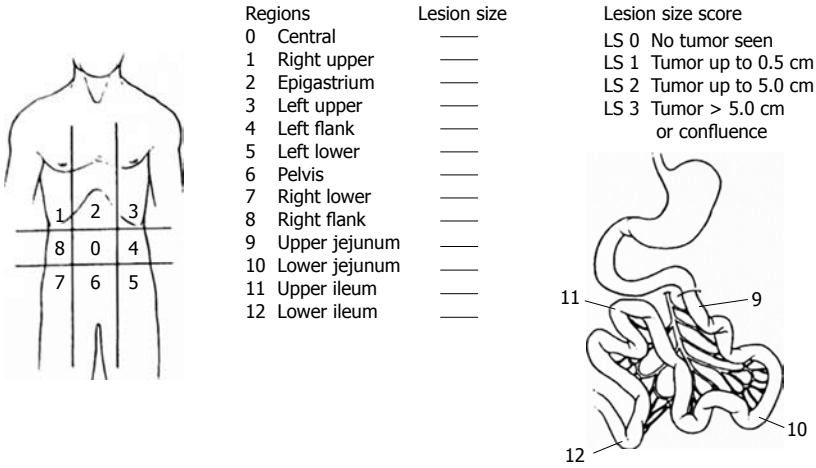

Figure 8 Peritoneal cancer index (PCI). Peritoneal cavity is divided into 13 parts, which ranges from 0 to 12. Accurate measurement of each region is scored as lesion size 0 through 3. LS 0: No implants. LS 1 refers to implants up to 0.5 cm in diameter; LS 2 refers to implants greater than 0.5 cm and up to 5 cm; and SL3 refers to those 5 cm or greater in diameter.

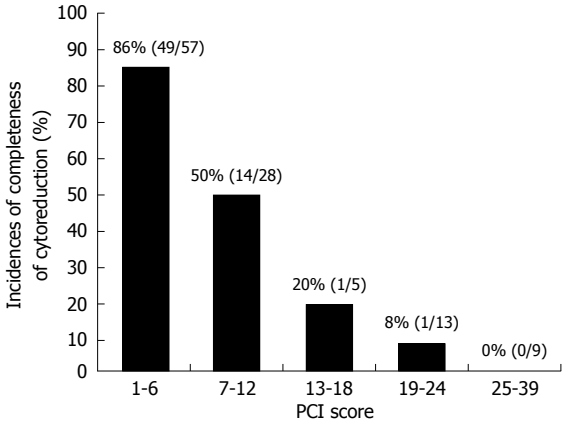

Figure 9 PCI scores and completeness of cytoreduction in 92 gastric cancer with PC, who underwent CRS.

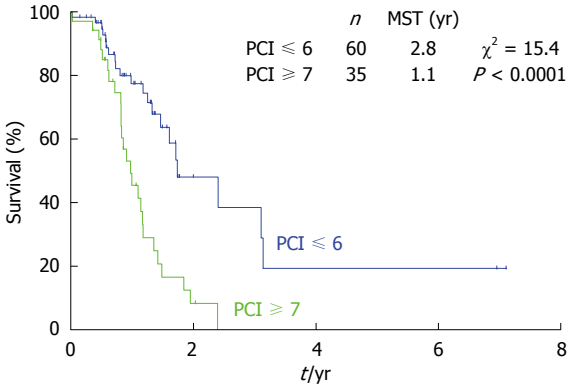

Figure 10 Survival differences of gastric cancer patients with PC, according to the PCI score.

rates of greater than 50%. In contrast, the depiction rate of small-bowel involvement had the lowest sensitivity, with a rate of 8%-17%. The sensitivity of CT for detecting PC was influenced by the lesion size and the false-negative rate significantly decreased with the lesion size. Small PC (< 0.5 cm) was visualized using CT with a sensitivity of 11%, in contrast to a sensitivity of 94% for PC with a diameter greater than 5 cm.

The diameter of PC from gastric cancer tends to be smaller than that from colorectal cancer because gastric cancer always has a poorly differentiated histological type. In our study, the PCI estimated from preoperative radiologic studies was compared with the intraoperative PCI score. The mean preoperative radiologic PCI and the operative PCI scores were 5.91 and 5.64 respectively (no statistical significance)[42]. Koh also reported that radiologically determined PCI underestimated the true extent of PC[38].

PET provides a functional image, but this modality has drawbacks for small lesions less than 5 mm in size. Although a PET-CT system seems to be an attractive option, the use of this modality is limited by its high cost as well as its limitations in the assessment of low-volume PC[42]. Since the accuracy of PET-CT for primary gastric cancer and lymph node metastases was 54%[43], PET is not recommended for the diagnosis of lymph node metastases from gastric cancer[43].

Yang *et al*[42] reported that the accuracy of PET-CT for PC from gastric cancer was 87%, with a sensitivity of 72.7%, a specificity of 93.6%, a positive predictive value of 82.1%, and a negative predictive value of 89.6%, and that PET-CT showed a better sensitivity than high-speed spiral CT (HSSCT). Because peritoneal deposits usually have a low-volume density, all radiological modalities have major limitations in the assessment of PC. Surgeons should keep in mind that the preoperative radiologic PCI scores are always smaller than the intraoperative PCI scores.

Recently, diagnostic laparoscopy has enabled the direct visualization of small PC but technical difficulties can arise in the presence of adhesions caused by prior surgery. Garofalo reported an excellent experience with laparoscopic diagnosis for PC[44]. A good correlation was obtained between the open surgery data and the laparoscopic PCI scores. This method exhibited an excellent diagnostic accuracy for PC on the small bowel mesentery which cannot be correctly diagnosed using CT, MRI or PET-CT.

HYPERTHERMIC INTRAPERITONEAL CHEMO-PERFUSION (HIPEC) AFTER CYTOREDUCTION

An abundance of experimental and clinical evidence has indicated that malignant cells are selectively destroyed by hyperthermia in the range of 41℃ to 43℃. Hyper-

thermia impairs DNA repair, protein denaturation and the inhibition of oxidative metabolism in the microenvironment of malignant cells and increases cell death[24,45-49]. Unfortunately, heat alone at such a low clinically applicable temperature cannot eradicate cancer cells because of a mechanism known as thermal tolerance that acts *via* the up regulation of heat shock protein[46]. However, hyperthermia enhances chemotherapy efficacy and the combination of heat and anti-neoplastic drugs frequently results in increased cytotoxicity. Some chemotherapeutic agents augment cytotoxicities in combination with mild hyperthermia. Such effects have been reported for mitomycin C, cisplatinum, docetaxel, gemcitabine and irinotecan[47-49]. An additional factor *in vivo* is increased drug penetration which is observed at temperatures above 39-42℃[49]. Los *et al*[17] reported that CBDA and cisplatinum penetrated 2-3 mm from the surface of experimental PC in rats but that penetration was limited to within 1-2 mm without hyperthermia.

Drug selection is very important when combined with hyperthermia. In HIPEC, a direct cytotoxic agent is needed. Anti-metabolites are not suitable because the duration of exposure is too short. Agents with large molecular weights have more favorable pharmacokinetics because of the delay in absorption resulting from the maintenance of high loco-regional concentrations in the peritoneal cavity. Rapid renal clearance may decrease side effects. Drugs that act synergistically with hyperthermia should be chosen. In HIPEC for gastric cancer, mitomycin C and CDDP, which have synergistic effects when used with hyperthermia, are typically used.

According to pharmacokinetic studies, approximately 70% of the administered mitomycin C is eliminated from the perfusate after 2 h of HIPEC[50]. With cisplatinum, 75% is lost from the perfusion fluid after a dwelling time of 90 min[51] and only 20% of the cisplatinum reaches the systemic circulation. The targeted tumor nodules may thus absorb a high proportion of this drug after 90 min of HIPEC. However, 30 min of HIPEC is probably too short for the optimal absorption of cisplatinum by the tumor nodules. Accordingly, 90-120 min might be more beneficial.

However, a long duration of HIPEC may increase the operation time and the incidence of morbidity. Yan *et al*[52] reported that a meta-analysis did not show a significant difference in the incidence of perioperative mortality between the HIPC and control groups. However, the meta-analysis did show a significant increase in the incidence of intra-abdominal abscess and neutropenia in the HIPEC group.

To date, intraperitoneal chemotherapy and hyperthermia have been investigated as possible treatment options for PC from ovarian, colorectal and gastric cancer. For advanced ovarian cancer, intraperitoneal chemotherapy in combination with CRS has been declared the standard practice[53]. For colorectal carcinomatosis, a randomized trial demonstrated a superior survival rate in patients receiving CRS and HIPEC, compared with traditional systemic chemotherapy and CRS[54,55]. In addition, the combination of CRS plus HIPEC has been

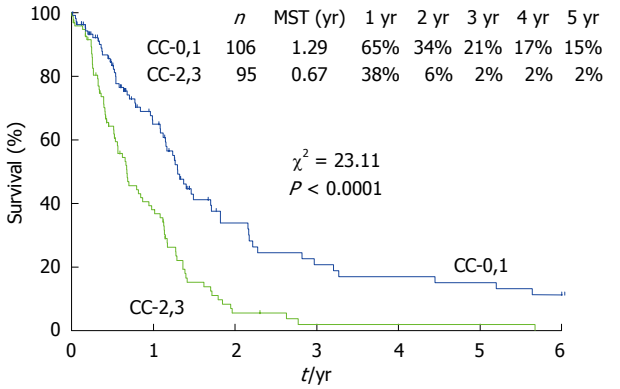

Figure 11 Survival curves of gastric cancer patients with PC after cytoreductive surgery and HIPEC using the CC score. The assessment of the CC is classified into 3 categories. CC-0: The complete cytoreduction with no residual macroscopic nodule; CC-1: No macroscopic tumor but positive margin histologically or suspicious residual nodules less than 5 mm; CC-2: Apparent macroscopic residual tumors greater than 5 mm but up to 5 cm; and CC-3: Residual PC greater than 5 cm in diameter.

suggested as the standard care recommended for PC from appendiceal cancer and mesothelioma. In gastric cancer, two randomized clinical trials (RCTs) have reported the prevention of peritoneal recurrence after curative resection[56,57]. A recent meta-analysis of RCTs for gastric cancer indicated that HIPEC with CRS is associated with an improved overall survival[52].

Figure 11 shows the survival curves for 211 patients with PC from gastric cancer who had been treated with CRS and HIPEC. Patients who received a CC-0 or CC-1 cytoreduction survived significantly longer than those who had received a CC-2 or CC-3 CRS. Before performing HIPEC, surgeons should remove as many PC nodules as possible. Because the depth of drug penetration is limited to 1-3 mm, the residual tumor burden should correspond to a status of CC-0 or CC-1. These results strongly suggest that HIPEC just after CRS can improve the survival of patients who have received a CC-0 or CC-1 cytoreduction. Gastric cancer spreads not only *via* transcoelomic routes, but also *via* lymphatic and hematogenous routes. Patients with both PC and distant lymph node metastasis, such as para-aortic lymph nodes or hematogenous metastasis, should be excluded from the indications for CRS and HIPEC.

As shown in Table 5, a multivariate analysis revealed that both NIPS and CC-0 or CC-1 were independent prognostic factors of a good prognosis after CRS plus HIPEC. The best indications for CRS + HIPEC are localized PC (PCI less than 6) from resectable gastric cancer that has been removed completely during a peritonectomy.

EARLY POSTOPERATIVE INTRAPERITONEAL CHEMOTHERAPY (EPIC)

EPIC is started during the early postoperative period as soon as the patient's physical condition allows. It is started at the time of minimal residual tumor burden

Table 5 Multivariate survival analysis of 90 patients with PC

Clinicopathologic factors	χ^2	*P*	Relative risk	95% CI levels
Sex (male *vs* female)	3.87	0.049	0.64	0.401-1.020
Age (≤ 65 *vs* > 65)	0.08	0.653	0.74	0.098-5.595
CC (CC-0,1 *vs* CC-23)	7.96	0.004	2.32	1.004-3.638
NIPS (done *vs* not done)	5.28	0.016	3.06	1.008-4.046
PCI (≤ 6 *vs* ≥ 7)	0.80	0.802	0.91	0.444-1.872
Histology (diff. *vs* poorly diff.)	0.59	0.442	0.62	0.252-4.399

From gastric cancer, treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) (cox proportional hazard model). PCI: Peritoneal cancer index.

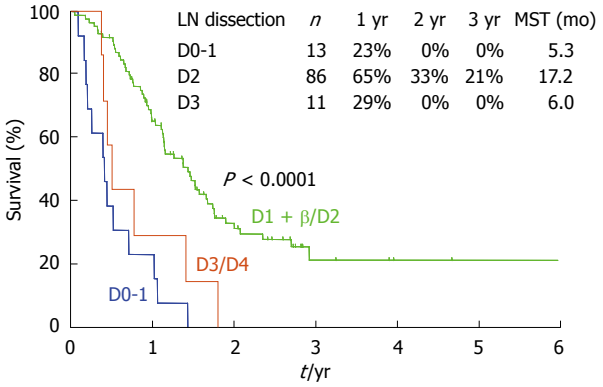

Figure 12 Survival curves of P0/Cy1 patients without distant metastasis, according to the extent of lymph node dissection.

before the residual cancer cells can become entrapped in postoperative fibrin deposits[11,58]. EPIC regimens with cell-cycle dependent drugs in 500 mL of saline are administered on postoperative days 1-5 through a catheter. Jeung *et al*[11] started EPIC on the day of operation using 5-FU (500 mg/m^2) and cisplatinum (40 mg/m^2, days 1-3) administered over a four weeks interval. The predominant toxicity was neutropenia and nausea/vomiting. The authors recommended EPIC for the treatment of patients with resectable gastric cancer with PC who had a good performance status (PS-0 of PS-1). Yu *et al*[59] performed an RCT consisting of 248 advanced gastric cancer patients treated with surgery plus EPIC (mitomycin-C plus 5-FU) and surgery alone. The surgery plus EPIC group had a superior overall survival, compared with the surgery alone group. In a subgroup analysis, the improvement in the survival rate was found to be statistically significant for patients with gross serosal invasion and lymph node metastasis. The authors recommended the use of EPIC for the treatment of stage 3 or 4 advanced gastric cancer patients with T3 or N+.

FAILURE ANALYSIS OF RECURRENT DISEASE FOLLOWING CRS AND PERIOPERATIVE INTRAPERITONEAL CHEMOTHERAPY

After complete cytoreduction and perioperative intraperitoneal chemotherapy for PC from colorectal cancer, about two thirds of patients experienced recurrences. The most common type of recurrence was a localized intra-abdominal recurrence and the median time for progression was 9 mo.

Unfortunately, approximately 75% of the patients who underwent a complete cytoreduction and HIPEC developed recurrences. In the 111 gastric cancer patients with PC who received CC-0 or CC-1 CRS and HIPEC, 65 patients experienced recurrences. The median survival period was 9.5 mo. Thirty-one (48%) and 51 (78%) of the patients died from recurrences at one and two years after CRS + HIPEC respectively. Four patients died of peritoneal (3 patients) or bone (one patient) recurrences 5-7 years after CRS + HIPEC. Thirty-seven patients had diffuse intraperitoneal recurrences, 5 had bone metastasis, 2 had lymph node recurrences and one had a skin recurrence.

For the treatment of localized intraperitoneal recurrences of colorectal cancer, surgical treatment, such as a second CRS, or intraperitoneal chemotherapy can result in long-term survival. In gastric cancer patients however, almost all recurrences are diffuse intraperitoneal recurrences. To prevent recurrence and prolong the survival of gastric cancer patients after CRS and HIPEC, EPIC and late systemic chemotherapy are mandatory.

Table 6 recurrence patterns after curative resection of P0/Cy1 patients *n* (%)

	Peritoneum	Lymph node	Liver	The others
Negative cytological status	42/92 (45.6)	20/92 (21.7)	23/92 (25.0)	7/92 (7.6)
Positive cytological status	22/27 (81.4)	2/27 (7.4)	2/27 (7.4)	1/27 (3.7)

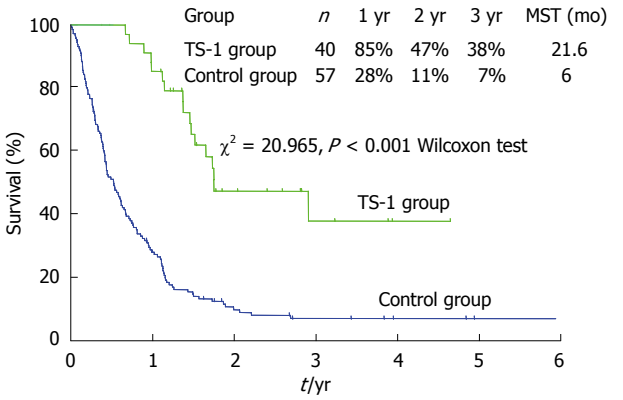

Figure 13 Survival of P0, Cy1 patients treated with gastrectomy+ postoperative TS-1 therapy and gastrectomy alone.

TREATMENTS FOR PATIENTS WITH A P0/CY1 STATUS

As already mentioned, a P0/Cy1 status means the absence of macroscopic PC but a positive cytological examination of peritoneal washing fluid. The survival of P0/Cy1

patients after gastrectomy is very poor, with a 5-year survival rate of less than 5% because of the persistence of micrometastases outside the surgical field. Since no effective chemotherapy regimens for PC have been reported, some Japanese surgeons do not recommend performing a gastrectomy for P0/Cy1 patients. In general however, a gastrectomy is believed to improve the survival of these patients. No reports describing the efficacy of lymph node dissection in P0/Cy1 patients have been made. As shown in Figure 12, patients who received a D2 dissection showed a superior survival outcome when compared with patients who received a D1 or D3 dissection. Furthermore, patients with D number ⩾ pN showed a significantly better survival outcome than those with D < pN. These results may indicate that lymph node dissection improves the survival of P0/Cy1 patients[35].

A bursectomy, used to resect peritoneal deposits within the omental bursa, is considered an essential procedure for gastric cancer surgery. Yamamura *et al*[60] studied the PFCCs and CEA or cytokeratin 20 mRNA signals in the omentum and other peritoneal zones in the same patients. CEA/cytokeratin 20 mRNA signals could be detected simultaneously in the omental bursa and zones other than the omentum. Accordingly, P0/Cy1 patients cannot be cured by a gastrectomy + omentobursectomy because invisible viable cancer cells persist after the omentectomy. They proposed that a routine bursectomy could be omitted from radical gastrectomy even for curable gastric cancer patients.

If P0/Cy1 patients are treated with NIPS (Figure 2), the PFCCs can be eradicated in two-thirds of the patients. Accordingly, P0/Cy1 patients should undergo NIPS followed by CRS.

As shown in Table 6, peritoneal recurrence is the main site of recurrence after curative resection for P0/Cy1 patients. Accordingly, a gastrectomy combined with chemotherapy to control peritoneal recurrences should be performed.

For the multimodal therapy of P0/Cy1 patients, Yonemura *et al*[61] reported the use of a combination therapy comprised of radical gastrectomy and postoperative S-1 therapy. After radical gastrectomy, 35 patients were treated with oral S-1 (80 mg/m^2) for 28 consecutive days followed by a 14-d rest. This schedule was repeated every 6 wk (S-1 group). The other 66 patients did not receive any chemotherapy (control group). The patients in the S-1 group survived significantly longer than those in the control group (Figure 13) ($P < 0.0001$). The two-year survival rates of the control and S-1 groups were 9% and 53%, respectively. Recurrences were not observed in 15 patients (43%) in the S-1 group and 3 patients (5%) in the control group. Peritoneal recurrences after S-1 treatment and in the control group were observed in 11 (31%) and 34 (52%) patients respectively ($P < 0.05$).

The Cox proportional hazard model showed that S-1 treatment was an independent prognostic factor and the relative risk of the S-1 treatment group was 0.17-fold lower than that of the control group. Major adverse reactions included myelosuppression and gastrointestinal toxicities but these effects were generally mild and no treatment-related deaths occurred. Thus, S-1 treatment appears to be a safe and effective postoperative chemotherapy treatment for patients with a P0/Cy1 status.

Yonemura *et al*[35] reported an effect of HIPEC in P0/Cy1 patients and the 5-year survival rate of 15 P0/Cy1 patients after gastrectomy plus HIPEC was 42%.

FUTURE PROSPECTS FOR THE TREATMENT OF PC FROM GASTRIC CANCER

The development of effective intraperitoneal chemotherapy regimens and new regimens of systemic chemotherapy is awaited. Recently, new molecules with important roles in the formation of PC have been reported and molecular targeting strategies for these molecules will soon be exploited. Surgeons should combine CRS and perioperative chemotherapy using new anticancer agents for patients with PC.

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TOPIC HIGHLIGHT

Antonio Macrì, MD, Professor, *Series Editor*

Peritoneal carcinomatosis of colorectal origin

Antonio Macrì, Edoardo Saladino, Vincenzo Bartolo, Vincenzo Adamo, Giuseppe Altavilla, Epifanio Mondello, Giovanni Condemi, Angelo Sinardi, Ciro Famulari

Antonio Macrì, Edoardo Saladino, Vincenzo Bartolo, Ciro Famulari, Department of Human Pathology, University of Messina, General Surgery Unit, 98125 Messina, Italy
Vincenzo Adamo, Giuseppe Altavilla, Department of Human Pathology, University of Messina, Medical Oncology Unit, 98125 Messina, Italy
Epifanio Mondello, Angelo Sinardi, University of Messina, Anesthesiology Unit, 98125 Messina, Italy
Giovanni Condemi, Ospedali Riuniti della Locride, Hospital of Siderno, Medical Oncology Unit, 89048 Siderno, Italy
Author contributions: Macrì A, Saladino E and Famulari C performed research; Macrì A, Saladino E, Bartolo V, Adamo V, Altavilla G, Mondello E, Condemi G, Sinardi A, and Famulari C analyzed the data; Macrì A, Saladino E and Famulari C wrote the paper.
Correspondence to: Antonio Macrì, MD, Professor, University of Messina, Department of Human Pathology, General Surgery Unit, Via Consolare Valeria, 98125 Messina, Italy. amacri@unime.it
Telephone: +39-90-2212678 Fax: +39-90-2212683
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Abstract

Peritoneal carcinomatosis is, after liver metastases, the second most frequent cause of death in colorectal cancer patients and at the present time, is commonly inserted and treated as a stage Ⅳ tumour. Because there is no published data that outlines the impact of new therapeutic regimens on survival of patients with peritoneal surface diffusion, the story of carcinomatosis can be rewritten in light of a new aggressive approach based on the combination of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Also if these treatment perhaps allow to obtain better results than standard therapies, we suggest, that a large prospective randomised control trial is needed to compare long-term and progression-free survival under the best available systemic therapy with or without cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

Key words: Colorectal cancer; Peritoneal carcinomatosis; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy

Peer reviewers: De-Liang Cao, MD, PhD, Associate Professor, Department of Medical Microbiology, Immunology, and Cell Biology Simmons Cooper Cancer Institute, Southern Illinois University School of Medicine 913 N. Rutledge Street, Springfield, IL 62794-9626, United States; Fahd Al-Mulla, PhD, Associate Professor, Department of Molecular Pathology, Kuwait University, Faculty of Medicine, Safat 13110, Kuwait

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INTRODUCTION

Peritoneal carcinomatosis (PC) is, after liver metastases, the second most frequent cause of death in patients with colorectal cancer (CRC). The peritoneal surface is involved in 10%-30%[1-3] of patients with CRC and in roughly 7%-8%[3,4] at the time of primary surgery, in 4%-19% of cases during follow-up after curative surgery, in up to 44% of patients with recurrent CRC who require relaparotomy, and in 40%-80% of patients who succumb to CRC[4]. However, in the 25% of patients with metastatic disease, the peritoneal cavity seems to be the only site of diffusion even after extensive diagnostic investigations[5].

Presently, this last group of patients is commonly classified and treated as stage Ⅳ CRC, and there is no published data that outlines the impact of new therapeutic

regimens on survival[6] and therefore research into new therapeutic approaches is widely justifiable and favourable.

NATURAL HISTORY OF PERITONEAL CARCINOMATOSIS

The PC occurs by a sequence of events: the spreading of cancer cells in the peritoneal cavity, their adhesion to the mesothelial surface and the invasion of the subperitoneal space for proliferation and vascular neogenesis[7]. The high incidence of tumour implantation on the peritoneal surface in CRC can be occur by intraperitoneal tumour emboli as result of serosal penetration, or can be the consequence of surgical management through leakage of the malignant cells from the lymphatic vessels or through their dissemination due to tumour trauma as result of dissection, with subsequent fibrin entrapment and tumour promotion of the entrapped cells[8].

The three principal studies[2,3,9] dedicated to the natural history of peritoneal carcinomatosis from CRC confirmed a poor prognosis with a median survival ranging between 6 and 8 mo and no 5-year survivors. Chu *et al*[2] reported, in a series of 100 patients with PC of nongynecologic tumours, a median survival of 6 mo. Sadeghi *et al*[3], in a multi-centre prospective study (EVOCAPE1) reported 118 patients with PC from CRC with a median survival of 5.2 mo. In a retrospective analysis[9] of 3019 patients with CRC, 13% of these presented carcinomatosis and had a median survival of 7 mo. Verwaal *et al*[10], in a phase Ⅲ randomized controlled trial of 50 patients who were treated with systemic chemotherapy and palliative surgery obtained an overall median survival of 12.6 mo with a 2-year survival rate of 18% and a median time to disease progression of 7.6 mo.

CYTOREDUCTIVE SURGERY (CRS) AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

As reported by Esquivel *et al*[6], in the light of a new aggressive approach based on the combination of CRS and HIPEC, the story of peritoneal carcinomatosis can probably be rewritten like the story of colorectal liver metastases.

In the 1930s, Meigs[11] was the first to advocate CRS followed by adjuvant radiotherapy in patients with ovarian cancer but with poor results. Subsequently Munnell[12] and Griffiths[13], between the 1960s and 1970s, demonstrated that better survival rates could be achieved by more extensive surgery and that the size of residual disease is the most important prognostic factor[11]. In 1980s, Spratt was the first to report, after an experimental study with hyperthermic peritoneal perfusion in dogs[14], the results of CRS followed by HIPEC using thioTEPA in a patient with pseudomyxoma peritonei[15]. After this first clinical report, Sugarbaker *et al*[16,17] finally in the 1990s proposed and improved CRS and perioperative intraperitoneal chemotherapy as a possible treatment, initially for peritoneal dissemination of the appendiceal neoplasms and diffuse malignant peritoneal mesothelioma[14] and successively, for patients with PC from various gastrointestinal tumours. This was based on the realization that PC is a form of locoregional cancer dissemination rather than a systemic spread of the disease.

RATIONALE AND TECHNIQUE OF CRS AND HIPEC

Perioperative intraperitoneal chemotherapy consists of the intraperitoneal administration of drugs in a large volume of fluid either during the operation or postoperatively[16]. Intraperitoneal chemotherapy can increase local exposure of the peritoneal surface to pharmacologically active molecules, especially those of high molecular weight (Mitomycin C, 5-FU, Doxorubicin, Cisplatin, Paclitaxel and Gemcitabine) resulting in a more uniform distribution throughout the abdominal cavity[16]. This treatment can also be performed under hyperthermic conditions. Hyperthermia associated with intraperitoneal chemotherapy, presents several advantages; it has a direct cytotoxic effect and enhances the activity and penetration depth of many cytotoxic drugs[17-19]. Because it is estimated that the optimal target of thermochemotherapy is limited to few millimetres, is mandatory to resect all the macroscopic disease[20,21]. According to Sugarbaker, the peritoneum can be divided into six parts, so between one and six peritonectomy procedures may be required, including visceral and parietal peritonectomies[22]. Subsequently, when the resection of the cancer is complete, some catheters and suction drains are placed through the abdominal wall to permit perfusion, with open or closed abdomen techniques or with peritoneal cavity expander or a semi-opened or semi-closed technique. The duration of the perfusion varies according to investigators and drugs used, from 30 to 120 min, and a heat exchanger keeps the infused fluid at 46-48℃ so that the intraperitoneal fluid is maintained at 41-43℃[23,24]. When the perioperative intra-abdominal chemotherapy is over, the abdominal cavity must be revisited. As to the timing of bowel anastomoses, pre- or post-hyperthermic chemotherapy, there is no consensus.

The best choice of drugs and their dosage for intraperitoneal therapy are still under discussion. Although Mitomycin-C is the most frequently used cytostatic agent, either alone or in combination with 5-FU or Cisplatin, recently others drugs like Oxaliplatin and Irinotecan have been studied alone or in combination. Elias, in a phase Ⅱ study, using Oxaliplatin after administration of 5-FU and Leucovorin iv before HIPEC, reported no case of mortality, 40% morbidity and a 5-year overall survival of 48.5% (median survival 60.1 mo) with a 73% rate of recurrence at 14 mo[25]. In another study, the same author, in a retrospective comparison of HIPEC with Oxaliplatin *vs* standard systemic chemotherapy, found that median survival rate of the HIPEC group was significantly better than that of the other group (62.7 mo *vs* 23.9 mo)[26].

EARLY POSTOPERATIVE INTRAPERITONEAL CHEMOTHERAPY

Another modality of perfusion is the early postoperative intraperitoneal chemotherapy (EPIC). In this technique, intraperitoneal chemotherapy is administered on postoperative days 1-5, and can be initiated immediately postoperatively and continued in the outpatient setting[27]. EPIC has the advantage that it can be performed anywhere and at anytime because it does not necessitate any special apparatus and this is most relevant and useful when the carcinomatosis is a fortuitous discovery during laparotomy[28]. Another advantage is the possibility to administer multiple cycles of chemotherapy[29]. But EPIC has many deficiencies, such as the failure to uniformly treat all the peritoneal surfaces, and to provide the additive effect of hyperthermia, the greater risk of significant systemic absorption and adverse effects of a high concentration of chemotherapy which increases the possibility of complications[23,24,27,28].

SURVIVAL AFTER CRS AND HIPEC

In the last decade, an increasing number of prospective studies investigated the effectiveness of the CRS and HIPEC in the management of peritoneal surface malignancies of colorectal origin. Verwaal *et al*[10] were the first who in 2003 conducted a randomized controlled trial comparing the efficacy of CRS and HIPEC with systemic chemotherapy and surgery. This trial clearly demonstrated longer survival in the combined treatment group with a median survival of 22.3 mo *vs* 12.6 mo obtained in the control arm. Subsequently, Glehen *et al*[28] in 2004, in a multi-institutional registry study from 28 international treatment centres, showed that the median survival was 19 mo and 3-year survival was 39% after CRS and HIPEC for 506 patients with colorectal peritoneal carcinomatosis. However at present, the clinical outcomes, in the literature, vary considerably: the median survival from 12 to 32 mo, with one-year, 2-year, 3-year and when reported 5-year survival rates ranging from 65% to 90%, 25% to 60%, 18% to 47% and 17% to 30%, respectively[4]. Univariate and multivariate analyses of most series of patients with PC of colorectal origin revealed several clinical, surgical and pathologic factors predictive of survival[4]. Clinical characteristics that have been correlated, in univariate analyses with an improved survival, are female gender, younger age and good clinical performance status[4]. Surgical factors that have been correlated with survival are the extent of carcinomatosis encountered at laparotomy, the completeness of resection, bowel obstruction, the presence of ascites and the presence and resection of metastatic disease to the liver[4]. Finally, the pathologic factors that have been correlated with impaired survival include site of the primary tumour, poor tumour differentiation, signet cell histology and lymph node involvement. However, the results of multivariate analyses on the abovementioned clinicopathologic factors were reported in 5 publications; in 4 of these, the extent of disease [measured by Peritoneal Cancer Index (PCI)] and the completeness of resection were the factors most related to treatment success and survival[4]. Patients with localization in six or seven regions of the abdomen had a poor prognosis, with a median survival of 5.4 mo *vs* 29 mo in those with a lower number of regions affected[7]. In a recent retrospective study, in 70 patients, da Silva and Sugarbaker demonstrated by univariate analysis, that the patients with a PCI < 20 had a median survival of 41 mo compared with 16 mo for patients with PCI > 20 (P = 0.004)[29].

Verwaal *et al*[10], using their seven regions system, demonstrated that the survival benefit was low in patients with more than five regions involved, with a greater correlated morbidity. The completeness of resection was also linked to survival. Median survival following complete resection of all macroscopic disease varied from 17.8 mo to 39.0 mo, whereas the reported 5-year survival rates varied from 20% to 54% while median survival, after incomplete resection, resulted in median survival times of 12.5-24 mo, with 5-year survival rates between 10% and 29%. When macroscopic disease of more 5 mm in diameter had to be left behind, the reported median survival varied between 5 and 12 mo and none of these patients survived for 5 years[4].

MORBIDITY AND MORTALITY AFTER CRS AND HIPEC

CRS followed by HIPEC carries a postoperative morbidity of 14% to 55% and a treatment-related mortality of 0% to 19%, which seem to be related to the extent of surgery as a function of peritoneal involvement rather than to the HIPEC[4]. Yan *et al*[30] suggested that there is a learning curve associated with the procedure for achieving an acceptable morbidity rate and Roviello affirms that postoperative complications could be resolved favourably in most cases with correct patient selection and adequate postoperative care[31]. We also want to underline, as already demonstrated in our recent manuscript[32], that 6 mo after surgery, the patients submitted to CRS and HIPEC, recover the same quality of life levels as the preoperative period.

CONCLUSION

A recent international conference was convened and a consensus statement on the appropriate use of CRS and HIPEC was developed and adopted by the Peritoneal Surface Malignancy Group in an attempt to standardize the indications and techniques for this treatment[6]. However we retain, according with the conclusion of Glockzin in his recent review[33], that a large prospective RCT is needed to compare long-term and progression-free survival under best available systemic therapy with or without CRS and HIPEC.

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Peritoneal carcinosis of ovarian origin

Anna Fagotti, Valerio Gallotta, Federico Romano, Francesco Fanfani, Cristiano Rossitto, Angelica Naldini, Massimo Vigliotta, Giovanni Scambia

Anna Fagotti, Valerio Gallotta, Federico Romano, Francesco Fanfani, Cristiano Rossitto, Angelica Naldini, Massimo Vigliotta, Giovanni Scambia, Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, 100168, Rome, Italy

Author contributions: Fagotti A designed the paper; Fagotti A, Gallotta V and Romano F wrote the paper; Fanfani F, Rossitto C, Naldini A and Vigliotta M performed data gathering; Scambia G was the responsible surgeon and supervised the paper.

Correspondence to: Anna Fagotti, MD, Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, L. go A. Gemelli, 100168, Rome, Italy. annafagotti@libero.it

Telephone: +39-6-30154979 Fax: +39-6-30154979
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Abstract

Epithelial ovarian cancer (EOC) is the second most common genital malignancy in women and is the most lethal gynecological malignancy, with an estimated five-year survival rate of 39%. Despite efforts to develop an effective ovarian cancer screening method, 60% of patients still present with advanced disease. Comprehensive management using surgical cytoreduction to decrease the tumor load to a minimum, and intraperitoneal chemotherapy to eliminate microscopic disease on peritoneal surface, has the potential to greatly improve quality of life and to have an impact on survival in ovarian cancer patients. Despite achieving clinical remission after completion of initial treatment, most patients (60%) with advanced EOC will ultimately develop recurrent disease or show drug resistance; the eventual rate of curability is less than 30%. Given the poor outcome of women with advanced EOC, it is imperative to continue to explore novel therapies.

Key words: Peritoneal carcinosis; Ovarian cancer; Intraperitoneal hyperthermic chemotherapy; Cytoreduction

Peer reviewer: Francesco Fiorica, MD, Department of Radiation Oncology, University Hospital S'Anna, Corso Giovecca 203, Ferrara I-44100, Italy

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INTRODUCTION

Epithelial ovarian cancer is the second most common genital malignancy in women and it is the most lethal gynecological malignancy, with an estimated five-year survival rate of 39%[1]. Despite efforts to develop an effective ovarian cancer screening method, 60% of patients still present with advanced (Stages Ⅲ-Ⅳ) disease[2]. CA-125 serum levels, transvaginal ultrasound, and pelvic examination have long been thought to be potentially effective screening tools. However, none of them have proved effective in decreasing mortality from ovarian cancer.

An epithelial ovarian tumor arises from the serosal lining of the ovary, which communicates with the serosal lining of the abdomino-pelvic cavity known as the peritoneum. As a consequence of tumor growth, malignant cells exfoliate and shed, becoming free floating in the peritoneal fluid. They typically implant in the pelvis and subdiaphramatic recesses owing to gravity and the incumbent position. This spread of the tumor within the peritoneum is termed peritoneal carcinomatosis, and it is a typical feature of cancer spread in patients with primary advanced or recurrent epithelial ovarian cancers. Intraoperatively, it is characterized by the presence of macroscopic tumor nodules of variable sizes and consistencies that can coalesce to form plaques or masses within

the abdominopelvic cavity. Tumor dissemination from the peritoneal cavity into the pleural cavity might also occur through the lymphatic lacunae within the diaphragmatic peritoneum. This results in severe pleural effusion which compromises lung and cardiac function. It typically presents with vague gastrointestinal symptoms, such as abdominal bloating, distension, weight loss, and fatigue. Due to the heterogeneity and lack of specificity of these early clinical symptoms, diagnosis is often delayed. In the final stages of this disease, patients suffer from severe symptoms of profound anorexia, dyspnea, and severe pain from malignant bowel obstruction, abdominal distension for ascites, and pleural effusion as a result of the extensive burden of tumors that characterizes this fatal deterioration. In the past, peritoneal carcinomatosis was considered a terminal condition and patients were treated with palliatively. However, despite extensive dissemination within the abdominopelvic cavity, this condition is now considered a loco-regional disease.

In many patients, the natural history of ovarian cancer is similar to gastrointestinal tumors with peritoneal surface dissemination. In fact, in both cases, the late consequences of peritoneal carcinomatosis are debilitating ascites and intestinal obstruction. With the full knowledge of the natural history of this progressive disease, the targets of the treatment should be both the peritoneal surface diffusion and the systemic metastases. There is no doubt that the eradication of the peritoneal surface components of this disease would be a major contribution to the overall, and disease-free, survival, as well as improving the quality of life of ovarian cancer patients. Comprehensive management using surgical cytoreduction to decrease the tumor load to a minimum, and intraperitoneal chemotherapy to eliminate microscopic disease on peritoneal surface, has the potential to greatly improve quality of life and have an impact on survival in these patients. In the setting of primary disease, optimal cytoreductive surgery (residual tumor < 1 cm) and platinum-based chemotherapy have been established as the most important determinants of clinical outcome.

THE CLINICAL AND BIOLOGICAL RATIONALE FOR MAXIMAL CYTOREDUCTION IN OVARIAN CANCER

More than 20 years after Griffiths' major paper[3], a recent meta analysis by Bristow *et al*[4] examined the effect of maximal cytoreductive surgery on survival in advanced ovarian cancer. The author concluded that maximal cytoreduction was one of the most powerful reasons of cohort survival for patients with this disease. Eisenkop *et al*[5] found that cytoreduction had a more significant influence on survival than the extent of metastatic disease observed before surgery. Incorporating extensive upper abdominal debulking procedures with standard pelvic cytoreduction (rectosigmoid resection, peritoneal stripping, diaphragm stripping, extensive bowel resection, splenectomy, partial gastrectomy, and resection of liver and kidney) not only significantly improved the disease-free survival rate of patients left with optimal residual disease (85%), but also led to a significant improvement in overall survival.

The apparent value of primary cytoreductive surgery is based on the following reasons: (1) Surgery is thought to remove resistant clones of tumor cells and thus decreases the likelihood of the early onset of drug resistance; (2) The removal of large masses likely to be associated with poorly vascularized areas of tumors supposedly improves the probability of delivering adequate drug doses to the remaining cancer cells; (3) The higher growth fraction in better vascularized small masses enhances the effect of chemotherapy; (4) In principle, smaller masses require fewer cycles of chemotherapy and thus decrease the likelihood of drug resistance; (5) Removal of bulky disease theoretically enhances the immune system; (6) The patients feel better after removal of ascites and large tumor masses, particularly from the omentum; and (7) Surgery alleviates the associated nausea and satiety these patients feel.

PREOPERATIVE SELECTION CRITERIA TO EVALUATE THE INTRAPERITONEAL DIFFUSION OF THE DISEASE

Residual disease after primary surgery is one of the most important prognostic factors in advanced ovarian cancer patients. However, a certain percentage of women, ranging between 25% and 90%[6,7], are not suitable for optimal cytoreduction after exploratory laparotomy, and are treated by neoadjuvant chemotherapy. To preoperatively identify patients with unresectable tumors, which can be spared an unnecessary exploratory laparotomy, several approaches have been attempted, including the evaluation of CA-125 serum levels and the radiological assessment of tumor spread. However, the accuracy of these parameters has been unsatisfactory, and has been limited by the retrospective nature of the studies and the highly variable rates of optimal cytoreduction in different series[7]. In this context, a genetic analysis by microarrays has been attempted to identify some biologic characteristics underlying the possibility of optimal debulking, resulting in a low predictive accuracy[8]. Laparoscopy is well known for offering a direct and magnified vision of the peritoneal cavity and a better view of the upper abdomen. It allows the pathological assessment of the disease without an open surgical procedure, with a shorter operating time, and better results in terms of postoperative morbidity. Indeed, it has been demonstrated to be an effective procedure for restaging early ovarian cancer[9-11]. A recent pilot study by Fagotti *et al*[12] demonstrated that laparoscopy is an adequate and reliable procedure for the assessment of the chances of optimal cytoreduction (RT < 1 cm) in clinically advanced ovarian cancer patients. Since then, other investigators have been confirming the role of laparoscopy in the evaluation of the possibility of achieving optimal residual disease in the same clinical subset[13,14]. Subsequently, in a consecutive prospec-

tive series of 113 advanced ovarian cancer patients, the presence of omental cake, peritoneal and diaphragmatic extensive carcinomatosis, mesenteric retraction, bowel and stomach infiltration, and spleen and/or liver superficial metastasis were investigated by laparoscopy. Each parameter received a score based on a specificity > 75%, positive predictive value (PPV), negative predictive value (NPV) > 50%, and accuracy > 60% with respect to the chances of achieving an optimal cytoreduction. By summing the scores relative to the presence of every aforementioned parameter, an overall laparoscopic value for each patient (total predictive index value = PIV) was calculated. Sensitivity, specificity, PPV, NPV, and accuracy with respect to optimal RT were calculated for each PIV. Finally, the authors concluded that the proposed laparoscopic model appears a reliable and flexible tool to predict optimal cytoreduction in advanced ovarian cancer. More recently, this model has been applied in a different center from that in which it was developed[15]. The results from this study have shown that even when utilized in a different setting of patients, the laparoscopic PIV can identify advanced ovarian cancer cases that are likely to be suitable for optimal debulking.

SURGICAL PROCEDURES IN THE MANAGEMENT OF ADVANCED OVARIAN CANCER

Worldwide, there are more than two hundred thousand new cases of ovarian cancer diagnosed annually, accounting for about 4% of female cancers.

In 1994, the National Institutes of Health[16] convened a 14-member panel of experts in the management of ovarian cancer to generate a consensus statement of recommendations. The panel concluded that: "Adequate and complete surgical intervention is a mandatory primary therapy for ovarian cancer, permitting precise staging, accurate diagnosis, and optimal cytoreduction. The procedure is best conducted by a qualified gynecologic oncologist, when there is a high probability of ovarian cancer. All women with suspected ovarian cancer should be offered a preoperative consultation with a gynaecologic oncologist". During the past decade, compelling published work has accumulated to lend support to these consensus recommendations. These reports show that initial surgery for ovarian cancer is most appropriately done by gynaecological oncologists, preferably in centers with expertise in the multidisciplinary management of this disease. Engelen *et al*[17] recently described a population-based observational study of patterns of care for 680 women with ovarian cancer in the northern Netherlands. The patients were treated between 1994 and 1997. The main objective of the study was the effect of surgery performed by a gynaecological oncologist on the quality of surgery and survival outcome compared with surgery by a general gynaecologist without subspecialty training. In all disease stages, patients received surgical treatment according to prevailing surgical guidelines more frequently when operated on by a gynaecological oncologist. The risk of death for patients who did not have surgery according to accepted guidelines was almost twice that for patients who had surgery according to the guidelines. In this study, patients with stage Ⅰ / Ⅱ disease were more likely to be staged by gynaecological oncologists than general gynaecological surgeons, resulting in a more accurate assignment of disease stage and administration of adjuvant treatment. For patients with stage Ⅲ disease, five-year survival was 32% when the guidelines were followed and 11% when guidelines were not (hazard ratio 1.97, 95% CI: 1.45-2.68, $P < 0.001$). Furthermore, more patients with stage Ⅲ disease had complete debulking (24% *vs* 12%) and reduced residual disease (< 2 cm) (62% *vs* 45%) by a gynaecological oncologist when compared to a gynaecologist. These data, as well as similar population-based studies, lend support to three main conclusions about the delivery of cancer care services for women with suspected ovarian cancer[18-21]: (1) the disparity in survival outcomes according to the specialty of operating surgeon, after confounding factors have been accounted for, supports the long-held hypothesis that the surgically-attained maximum diameter of residual disease is inversely proportional to survival outcome. Consequently, primary cytoreductive surgery offers the best opportunity for achieving extended survival and should be considered the standard of care for women with advanced-stage epithelial ovarian cancer; (2) the consistent and positive effect of a surgeons' specialty on survival provides irrefutable evidence that surgical care in ovarian cancer should be concentrated in centers with gynaecological oncologists. These surgical subspecialists have the necessary expertise to stage patients with early-stage disease as well as to perform the cytoreductive surgery necessary to achieve minimal residual disease in patients with advanced-stage tumors. Adequate and complete initial intervention is among the most powerful clinician-driven determinants of survival for women with ovarian cancer; and (3) the above conclusions call for widespread and consistent support by the medical community and governmental organizations in recognising specialty training in gynaecological oncology as a necessary component for comprehensive health care for women[22].

The standard of therapy in patients with advanced ovarian cancer is the surgical exploration of the pelvis and the upper abdomen and a maximum cytoreduction. The aim of surgery is to remove all tumor-infiltrated organs including the peritoneum, bowel, spleen, hepatic tissue *etc*., thus surgery is not limited to the pelvis, the omentum and the lymph nodes. Bristow *et al*[23] showed that even in patients with un-resectable liver metastasis, optimal de-bulking of extra-hepatic disease is associated with a significant survival advantage. Therefore, the intent of surgery is not to leave any macroscopic intraabdominal disease[24]. In a high percentage of patients, this aim can be reached by an encouraged, ultraradical, consequent, multivisceral surgery. Eisenkop *et al*[24] achieved 85% of optimal cytoreduction in a series of 163 patients with

stage Ⅲ and Ⅳ ovarian cancer. In our opinion, the limit of resectability can be defined by the extent of miliaric carcinomatosis on the serosa of the small bowel and by the infiltration of the major abdominal vessels. In conclusion, we should answer a crucial question to support the role of cyto-reduction in the management of advanced ovarian cancer: is attainment of an optimal outcome largely related to philosophy and skill of the surgeons or does it reflect a less aggressive tumor biology? These issues are still being studied and debated after more than 20 years. We believe that the better understanding of tumor biology can help in the planning of surgical strategy in cases of recurrent ovarian cancer, but the patient's general health, the presence of diffuse carcinomatosis, and the surgical philosophy are correlated with the achievement of an optimal surgical outcome.

NOVEL APPROACHES AND THE ROLE OF INTRAPERITONEAL CHEMOTHERAPY IN THE MANAGEMENT OF ADVANCED OVARIAN CANCER

Only about 50% of patients show a complete clinical response to systemic platinum/taxol based chemotherapy, and 30% of them have microscopic metastasis at second look surgery. Despite achieving clinical remission after completion of initial treatment, most patients (60%) with advanced epithelial ovarian cancer will ultimately develop recurrent disease or show drug resistance, and their rate of curability is less than 30%. The recurrence rate ranges between 30% and 50% for patients who show no lesion at the time of second look surgery[25]. In these patients, the median disease-free survival is only 24 mo.

These factors are major limitations in treatment of patients with ovarian cancer[26]. Different treatment modalities have been attempted to overcome these limits, such as secondary cytoreduction, second-line chemotherapeutic drugs, high-dose chemotherapy, intraperitoneal chemotherapy (IP), radiotherapy, immunotherapy, and hormone therapy. In fact, it is conceivable that recurrences in platinum-responsive patients might be prevented by higher doses of drugs to eradicate less sensitive clones of tumor cells that became resistant to platinum when lower doses are given during initial treatment[27].

To date, except for IP chemotherapy, none of these approaches has been found to have a significant impact on survival. IP chemotherapy refers to the administration of cytotoxic agents directly at the predominant disease site: the peritoneal cavity. The rationale is that a higher concentration of cytotoxic drugs and longer duration of exposure can be achieved while reducing the toxicity normally associated with intravenous therapy. In fact, cytotoxic drugs administered IP can directly target tumor masses confined to the abdominal cavity, thus bypassing the poor vascularization of small-volume disease and, therefore, increasing peri- and intra tumoral drug concentration. Cisplatin can penetrate small-volume tumors to a maximum depth of 1-3 mm; therefore, a benefit of this schedule can be obtained only for patients with microscopic residual disease. By the use of large doses of intraperitoneal cisplatin, the surface of the tumor can be exposed to high concentrations of cisplatin with a sufficient amount of drug leaking into the circulation. Thus, the level of drug reaching the tumor through capillaries is doubled compared with a maximally tolerated dose of cisplatin delivered intravenously[28].

Two large phase Ⅲ trials published in 1996 and 2001 have documented some outcome advantages for IP therapy[29,30]. Recently, a 3rd randomized trial showed that IP chemotherapy provides better long-term outcome than Ⅳ drug delivery in patients with advanced ovarian cancer[31]. In the United States, the National Cancer Institute and the Society of Gynecologic Oncologists have endorsed the use of intraperitoneal chemotherapy in recent position papers. However, some concerns have been raised about the use of IP therapy: (1) the effectiveness of IP therapy depends on uniform drug distribution. It is essential that fluid circulates freely throughout the peritoneal cavity. After cytoreductive surgery, the risk of IP adhesion formation is increased, which might limit the access of the active drug to the tumor areas; and (2) various complications have been attributed to IP catheter, such as infections.

The intraoperative administration of intraperitoneal chemotherapy has been designed to overcome such obstacles. The use of intraoperative intraperitoneal chemotherapy avoids the pitfalls of postoperative adhesions and inconsistent drug distribution. Overall, intraoperative chemotherapy allows optimal drug distribution to all peritoneal surfaces. This produces a regional pharmacokinetic advantage with the amount of drug delivered to the tumor greater than that delivered systemically.

Intraperitoneal hyperthermic chemotherapy (HIPEC) is a new treatment modality that is based on increasing the sensitivity of cancer cells to the direct cytotoxic effect of chemotherapeutic agents at high temperature and increasing the concentration of chemotherapeutic agents that penetrate cancer tissues[32-34]. In fact, it has been proved that high temperature damages cancer cell membranes and promotes cellular apoptosis by increasing the intracellular calcium concentration and DNA fragmentation. Another mechanism is the destabilization of thymidine kinase 1, which is involved in DNA synthesis in cancer cells[35]. At 42℃, hyperthermia is cytotoxic by itself, increasing membrane permeability, inhibiting DNA repair, and promoting macrophage lysosomal exocytosis with consequent apoptosis[36]. The treatment modulates the activity of cytokines[37], and increases the antigenicity of tumor cells by the production of heat shock proteins and the activation of natural killer cells[38]. In conclusion, the biophysical effects of HIPEC are: membrane protein denaturation, increased vascular permeability, and alterations of multimolecular complex for DNA synthesis and repair. Moreover, the architecture of the vasculature in solid tumors is chaotic, resulting in regions with low pH, hypoxia, and low glucose levels. This

microenvironment makes solid tumors more susceptible to hyperthermia[39].

Cisplatin has been shown to penetrate deeper into tumor tissue under hyperthermic conditions compared to normothermic conditions. At 40-43℃, neoplastic cells become more chemo-sensitive due to an enhancement of intracellular concentrations of drugs and to alterations in the DNA repair process, especially for alkylating agents[40,41]. In addition, it has been shown that these events have a greater intensity in cisplatin-resistant rather than cisplatin-sensitive ovarian cancer cells lines. Formation of platinum-DNA adducts after cisplatin exposure is enhanced in heated cells, thus resulting in relatively greater DNA damage[42].

The critical point of this approach is cytoreduction down to nodules of less than few millimetres, to allow HIPEC to act. The possible synergy between hyperthermia and chemotherapy agents has sparked clinical trials utilizing this combination in many disease types. With regard to situations analogous with ovarian carcinoma, in which the disease may be widespread within the peritoneal cavity, studies in gastric cancer, malignant mesothelioma, appendix cancer, and colorectal cancer have shown promising results. A phase Ⅲ randomized study of hyperthermic intraperitoneal chemotherapy following cytoreductive surgery compared with traditional iv chemotherapy in patients with peritoneal spread of colorectal carcinoma showed a statistically significant prolongation of life in the experimental arm[43]. In addition, this combined treatment has been suggested as the standard of care for peritoneal dissemination from neoplasm of the appendix[44,45] and diffuse malignant peritoneal mesothelioma[46]. With long-term follow-up, cytoreductive surgery plus HIPEC is the only treatment associated with a cure for these diseases.

EOC is a logical target for directed intraperitoneal therapy in combination with heat, and there are reports of clinical studies looking at hyperthermic intraperitoneal chemotherapy following surgical debulking in this disease[47-56]. In 2001, Hager *et al*[54] reported that HIPEC significantly increased the survival and response rates, and improved the quality of life, in 36 stage Ⅲ and Ⅳ ovarian cancer patients who showed resistance to systemic chemotherapy. Deraco *et al*[57] reported that HIPEC significantly increased two-year survival to 55% and delayed tumor progression in 27 patients with recurrent ovarian cancer after extensive surgery to nodules less than 2.5 mm in diameter. Nevertheless, the few clinical studies looking at HIPEC following surgical debulking suffer from some limitations: relatively small numbers of patients, retrospective studies, different clinical settings and drugs. In fact, published data show that different groups of patients have been often mixed together, in terms of number of recurrence (persistent, first, second, and third), type of recurrence (single, multiple, and carcinosis) and PFI (platinum-sensitive or -resistant). More recently, we reported an interesting series on the use of HIPEC and cytoreductive surgery in a specific setting of patients, where ovarian cancer women at their first recurrence with a PFI of at least 6 mo presented to a gynecological oncology referral centre[58]. All cases were strictly selected before inclusion in the protocol, utilizing AGO-DESKTOP Ⅱ criteria for secondary cytoreduction and performing an FDG-PET/CT and S-LPS in all cases before attempting surgery. The preoperative evaluation allowed a complete cytoreduction in 100% of the patients (23 CC-0 and two CC-1), that is an excellent result when compared to 50% of complete cytoreduction shown in a recent meta-analysis on secondary surgery[4]. As might be expected, this satisfying result was achieved at the cost of multiple organ resections, but peri-operative mortality and morbidity rates were 0% and 30%, respectively, which are well balanced with data reported in the recent literature, even if cytoreductive surgery alone is considered[59]. In conclusion, considering the potential advantages of HIPEC associated with cytoreductive surgery and the low morbidity and mortality rates, such a promising approach should be encouraged for long-term survival in platinum-sensitive recurrent ovarian cancer patients. We await larger prospective randomized studies with longer follow-up times.

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REVIEW

A pharmacological review on intraperitoneal chemotherapy for peritoneal malignancy

Tristan D Yan, Christopher Qian Cao, Stine Munkholm-Larsen

Tristan D Yan, Stine Munkholm-Larsen, Department of Cardiothoracic Surgery, University of Sydney, Royal Prince Alfred Hospital, 50 Missenden Road, Camperdown, NSW 2050, Australia
Christopher Qian Cao, Department of Surgery, John Hunter Hospital, Newcastle, NSW 2305, Australia
Author contributions: All of the authors participated in designing the study, drafting, editing and revising the article; All authors approved the manuscript.
Correspondence to: Tristan D Yan, BSc (Med), MBBS, PhD, Department of Cardiothoracic Surgery, University of Sydney, Royal Prince Alfred Hospital, 50 Missenden Road, Camperdown, NSW 2050, Australia. tristan.yan@unsw.edu.au
Telephone: +61-2-95150111 Fax: +61-2-95158184
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Abstract

Perioperative intraperitoneal chemotherapy in combination with cytoreductive surgery has been shown to be of benefit for treating selected patients with peritoneal surface malignancy. It has become a new standard of care in the management of diffuse malignant peritoneal mesothelioma and peritoneal dissemination of appendiceal malignancy. Numerous recent publications on carcinomatosis from colorectal cancer and gastric cancer identify groups of patients that would benefit from this local-regional approach for prevention and treatment of carcinomatosis. This review focuses on pharmacological information regarding intraperitoneal chemotherapeutic agents commonly used in gastrointestinal oncology.

Key words: Intraperitoneal chemotherapy; Mitomycin C; Doxorubicin; Cisplatin 5-fluorouracil; Paclitaxel; Peritoneal surface

Peer reviewer: Tomomitsu Tahara, MD, PhD, Department of Gastroenterology, Fujita Health University, Dengakugakubo, Kutsukakecyo, Toyoake, Aichi 470-1192, Japan

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INTRODUCTION

In the past, pseudomyxoma peritonei, diffuse malignant peritoneal mesothelioma and peritoneal carcinomatosis from gastrointestinal cancer were considered lethal conditions without curative treatment options. Over the last two decades, multi-modality treatments have evolved. Increasing utilization of cytoreductive surgery combined with intraperitoneal chemotherapy as a treatment strategy for the management of peritoneal dissemination of these malignancies has been regularly reported[1-15]. Benefits have been universally documented in phase II studies. However, as of this point in time, a uniformity of the management for prevention or treatment of peritoneal surface malignancy using perioperative intraperitoneal chemotherapy has not been reached (Table 1). This review focuses on the pharmacological information available for intraperitoneal chemotherapeutic regimens.

Both pseudomyxoma peritonei and diffuse malignant peritoneal mesothelioma tend to remain localized within the abdominopelvic cavities and extraperitoneal metastasis is rarely seen. Pseudomyxoma peritonei is characterized by abundant mucinous tumor masses combined with copious mucus ascites. The cancer cells accumulate at non-mobile anatomic sites or gravity dependent areas. In contrast, the surfaces of the small bowel and its mesentery may remain free of disease[16]. Diffuse malignant peritoneal mesothelioma arises from the serosal lining of the abdominal cavity[7]. It is characterized by a diffuse pattern of tumor nodules throughout the peritoneal cavity.

Peritoneal implants are present in 10% of patients with colorectal cancer at the time of diagnosis[17]. Isolated peritoneal carcinomatosis of colorectal cancer is a result

of transcoelomic dissemination. The cancer cells penetrate through the full thickness of the colonic bowel wall, gain access to the peritoneal space, implant and grow on the peritoneum. Peritoneal involvement tends to be more extensive immediately surrounding the primary tumor.

Sugarbaker described the concept of "tumor cell entrapment". In this hypothesis, cancer cells gain access to the peritoneal cavity as a result of surgical trauma to a cancer specimen. During the early postoperative period the cancer cells become entrapped by fibrin and are stimulated by inflammatory growth factors released during the healing process[18]. As a result of this mechanism of cancer dissemination, approximately 30% of gastric cancer patients after gastrectomy will develop resection site disease or peritoneal seeding.

RATIONALE FOR PERIOPERATIVE INTRAPERITONEAL CHEMOTHERAPY

Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy is indicated in a majority of patients with diffuse malignant peritoneal mesothelioma and pseudomyxoma peritonei and in selected patients with peritoneal dissemination of colorectal cancer and gastric cancer. The fundamental goal of intraperitoneal chemotherapy administration is to maximize the total amount of drug delivered into the peritoneal tumor nodules while minimizing that delivered to the systemic circulation. The cytotoxic effects on peritoneal cancer nodules are the result of direct physical contact with intraperitoneal chemotherapy followed by penetration by diffusion. These events are influenced by the drug concentration in the chemotherapy solution, the ability of the drug to penetrate the tumor and the rate of elimination of the drug from the tumor nodules into the systemic circulation by capillary blood flow. Both natural or acquired drug resistance are important considerations in the long-term outcome of these treatments.

Physical properties of perioperative intraperitoneal chemotherapy

The physical-chemical properties of chemotherapeutic agents administered intraperitoneally should have larger, hydrophilic and ionized compounds. These molecules tend to clear more slowly from the peritoneal cavity than smaller, lipophilic and unionized compounds[19]. Therefore, the drugs selected for intraperitoneal administration tend to maintain a significantly greater concentration over a longer period of time in the peritoneal fluid than in plasma. This increases the exposure of the tumor nodules to a maximal dose of intraperitoneal chemotherapy, without necessarily an increase in systemic toxicity.

Mechanism of drug penetration

When drugs are delivered *via* the intraperitoneal route, they penetrate tumor nodules by passive diffusion. Active transport has not been shown to be important in intraperitoneal chemotherapy gaining access to the tumor nodules. The depth of penetration achieved by passive diffusion is limited. Experiments suggest that the depth of penetration may be only a few cell layers to perhaps 2 to 3 mm[20]. As a result, the greatest clinical benefit will only occur in patients having complete eradication of all macroscopic disease by surgery. The smallest possible tumor nodules remain to be eradicated by intraperitoneal chemotherapy.

Timing of perioperative intraperitoneal chemotherapy

The timing of intraperitoneal chemotherapy administration is critically important in achieving the best therapeutic outcomes. Currently, two time periods are utilized for intraperitoneal administration - intraoperative and early postoperative. Drugs selected for intraoperative use generally have three requirements. They are augmented by heat and can cause a cytotoxic effect to cancer cells within 60 to 90 min independent of cell division[21,22]. Heat is used because it has a direct cytotoxic effect on cancer cells. In addition, hyperthermia causes an important augmentation of cell kill by certain drugs; consequently it may markedly increase regional cytotoxicity of the chemotherapeutic agents (Figure 1). Third, and perhaps most importantly, heat increases the penetration of chemotherapy into cancer cells (Figure 2).

The combination of intraperitoneal chemotherapy used in the operating room with hyperthermia has been referred to by many different names: Heated intraoperative intraperitoneal chemotherapy (HIIC); Intraperitoneal hyperthermic chemotherapy (IPHC); or Hyperthermic intraperitoneal chemotherapy (HIPEC). In this review, HIIC was used.

In the early postoperative period, before the inevitable postoperative intraabdominal adhesive process occurs, chemotherapy can be delivered and drained *via* intraperitoneal catheters. During the first 7 postoperative days the dwell may be continued for 12 to 24 h. Its distribution is relatively uniform throughout the abdominal cavity. This plan for chemotherapy administration is known as "early postoperative intraperitoneal chemotherapy (EPIC)". The drugs should have a large molecular weight so that they are maintained within the peritoneal cavity for a longer period of time. EPIC is usually continued for several days, and consequently cell cycle specific drugs can be used[17].

HEATED INTRAOPERATIVE INTRAPERITONEAL CHEMOTHERAPY

Mitomycin C

Mitomycin C is the most common agent used for HIIC in the treatment of patients with peritoneal carcinomatosis from appendiceal and colorectal cancers and is used in conjunction with other drugs for gastric malignancy. It is an antitumor antibiotic, with approximately 90% of the drug absorbed within the 90-min intraperitoneal irrigation. Its molecular weight is 334 and the area under the curve ratio between intraperitoneal concentration over plasma concentration times time is approximately 30 (Figure 3)[23]. The depth of tissue penetration achieved by mitomycin C

Table 1 Major series on IPHC and/or EPIC after cytoreductive surgery for PMP, DMPM, and CRPC

Chief investigator	Year	Treatment center	Type	*n*	Intraperitoneal chemotherapy	Survival (%)	
						3-yr	5-yr
Piso *et al*[1]	2001	Hanover, Germany	PMP	17	IPHC: cisplatin	75	-
Butterworth *et al*[2]	2002	Vancouver, Canada	PMP	11	EPIC: 5-FU + mitomycin	60	-
Witkamp *et al*[3]	2001	Amsterdam, Netherlands	PMP	46	IPHC: mitomycin	81	-
Sugarbaker *et al*[4]	2001	Washington, USA	PMP	501	EPIC: 5-FU + mitomycin IPHC: mitomycin	-	80
Loggie *et al*[5]	2001	Winston-Salem, USA	DMPM	12	IPHC: mitomycin	50	-
Sebbag *et al*[6]	2000	Washington, USA	DMPM	33	IPHC: cisplatin + doxorubicin	56	47
Sugarbaker *et al*[7]	2003	Washington, USA	DMPM	68	IPHC: cisplatin + doxorubicin EPIC: paclitaxel	60	50
Feldman *et al*[8]	2003	Bethesda, USA	DMPM	49	IPHC: cisplatin ± paclitaxel	-	59
Fujimura *et al*[9]	1999	Kanazawa, Japan	CRPC	14	IPHC: cisplatin + mitomycin + etoposide	21	-
Witkamp *et al*[10]	2001	Amsterdam, Netherlands	CRPC	29	IPHC: mitomycin	23	-
Elias *et al*[11]	2001	Villejuif, France	CRPC	64	IPHC: mitomycin ± cisplatin EPIC: mitomycin + 5-FU	47	27
Pestieau *et al*[12]	2000	Washington, USA	CRPC	104	IPHC: mitomycin EPIC: 5-FU	45	30
Zoetmulder *et al*[13]	2002	Amsterdam, Netherlands	CRPC	94	IPHC: mitomycin	-	30
Shen *et al*[14]	2004	Winston-Salem, USA	CRPC	77	IPHC: mitomycin	25	17
Glehen *et al*[15]	2004	Multi-institutions	CRPC	506	IPHC or EPIC	-	-

IPHC: Intraperitoneal hyperthermic chemotherapy; EPIC: Early postoperative intraperitoneal chemotherapy; PMP: Pseudo-myxoma peritonei; DMPM: Diffuse malignant peritoneal mesothelioma; CRPC: Colo-rectal peritoneal carcinomatosis.

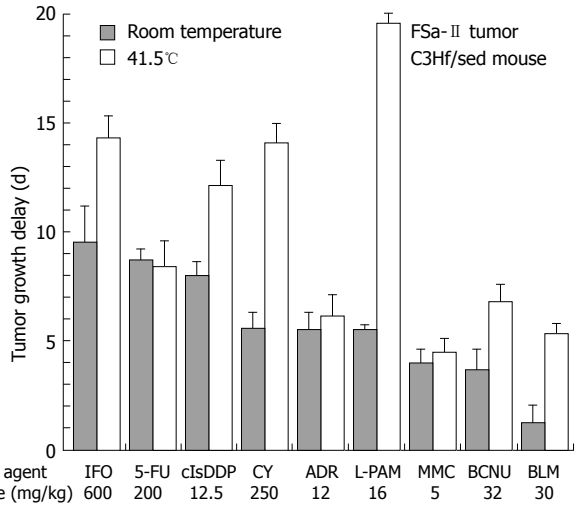

Figure 1 Tumor growth time with intraperitoneal chemotherapy alone *vs* heated intraperitoneal chemotherapy at 41.5℃. Tumor growth is delayed in heated intraperitoneal chemotherapy.

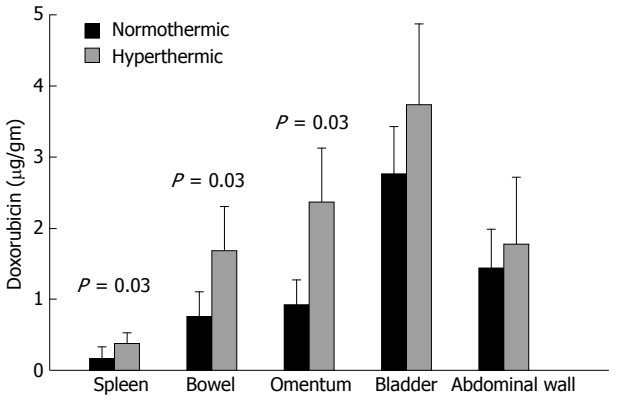

Figure 2 Heat increases the penetration of intraperitoneal chemotherapy into tissues. Modified from reference[53].

is up to 6 cell layers. It is rarely administered intravenously, as it has a high systemic toxicity profile. The renal toxicities of this drug can be prevented with forced diuresis intraoperatively and the hemolytic uremic syndrome has never been reported following intraperitoneal administration. Mitomycin C has potential adverse effects on wound healing, which can contribute to bowel perforation from anastomotic leak or fistula formation[24,25].

Currently, there has been a standardized dosage of mitomycin C established. In Amsterdam, it is administered at 30 mg/m^2 to 40 mg/m^2 as a single agent. In Washington, when combined with EPIC 5-fluorouracil the dose is recommended at 15 mg/m^2. Data regarding long-term survival reflecting the dose-response effects of intraperitoneal mitomycin C are difficult to interpret[26]. Some confusion regarding dosimetry and toxicity may be clarified by a recent study on pharmacokinetic changes induced by the volume of chemotherapy solution. In patients treated with hyperthermic intraperitoneal mitomycin C, the volume of carrier solution has a direct effect on systemic toxicity. Not only the dose of mitomycin C, but also the volume of chemotherapy solution should be determined by the patients' body surface area (Figure 4)[27]. Based on this study, a standardized protocol involving 15 mg/m^2 of mitomycin C in 1.5 L/m^2 carrier solution for all patients has been implemented at the Washington Cancer Institute in order to achieve maximal therapeutic effects and more predictable systemic toxicities. This dose of HIIC mitomycin C is routinely combined with 600 mg/m^2 per day for 5 d of 5-fluorouracil.

Results of treatment with mitomycin C

Xu and colleagues have recently suggested, in a meta-analysis, an improved management of advanced gastric

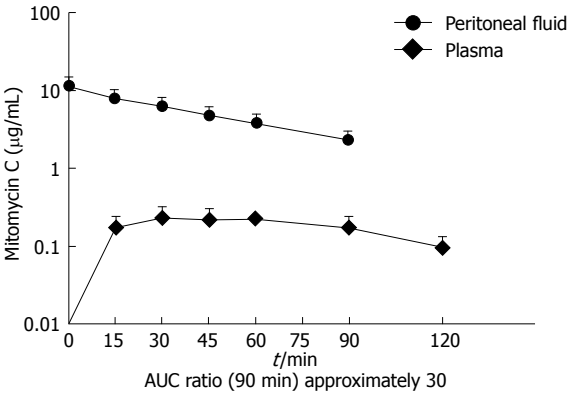

Figure 3 HIIC with MMC. The area under the curve ratio of intraperitoneal concentration over plasma concentration times time of heated intraoperative intraperitoneal mitomycin C is approximately 30. HIIC: Heated intraoperative intraperitoneal chemotherapy.

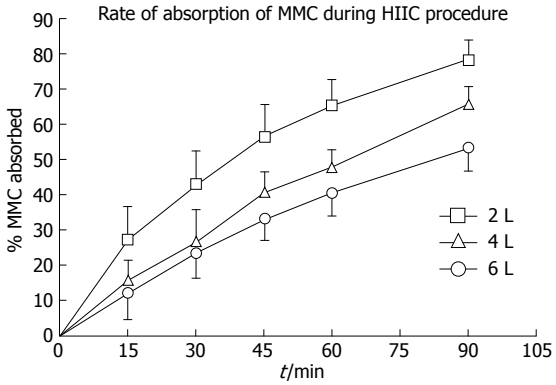

Figure 4 Absorption of mitomycin C from a hyperthermic solution containing 2, 4 or 6 L of 1.5% dextrose peritoneal dialysis solution. Cited form reference[27].

cancer when HIIC is used in conjunction with complete resection (Hazard ratio: 0.51 and 95% confidence interval: 0.40-0.65)[28]. In 8 of the 11 studies, mitomycin C was used. Results of treatment with colorectal carcinomatosis patients who entered in a phase Ⅲ randomized study of HIIC with mitomycin C have been reported by the Netherlands Cancer Center[15]. Patients with colorectal carcinomatosis were randomized to undergo systemic 5-fluorouracil/leucovorin therapy with or without palliative surgery versus cytoreduction, HIIC and systemic chemotherapy. A median survival of 12.6 mo was seen in the control arm, whereas the median survival of the HIIC arm was 22.3 mo (P = 0.032). The improved survival results from combined treatment with cytoreductive surgery and HIIC cannot be attributed to the effect of HIIC alone. However, at least in part, HIIC with mitomycin C has contributed to the prolonged median survival of colorectal carcinomatosis patients.

Doxorubicin

Doxorubicin is another antitumor antibiotic and is one of the earliest intraperitoneal chemotherapeutic agents used in clinical trials. Its molecular weight is 580 and the area under the curve ratio of intraperitoneal to intravenous concentration times time is 230. It is metabolized as a single pass through the liver so there is a low likelihood of systemic toxicities. Doxorubicin is augmented with heat and tissue penetration is at least five cell layers. This drug is ideally suited for intraperitoneal administration after a maximal attempt of cytoreduction[29,30]. It can also be used effectively with other intraperitoneal drugs, such as cisplatin and mitomycin C without pharmacological incompatibility.

Doxorubicin has a sclerosing effect on peritoneal surfaces. Sugarbaker and co-workers conducted a dose escalation study with pharmacokinetic monitoring of intraperitoneal doxorubicin and they demonstrated that a total dose of 15 mg/m^2 results in a thin layering of fibrosis on the peritoneal surfaces. These adhesions are not extensive enough to cause abdominal pain or intestinal obstruction[31,32]. With the proper dosage, this sclerosing effect can be used for treating patients with debilitating ascites when combined with cisplatin (50 mg/m^2). At the Washington Cancer Institute, this combination at 41.5℃ in 1.5 L of chemotherapy solution is a standard regime for patients with diffuse malignant peritoneal mesothelioma[33].

Recent pharmacokinetic studies demonstrated that the doxorubicin content in small mesothelioma nodules far surpassed that measured in the peritoneal fluid (Figure 5). An active uptake of doxorubicin by mesothelioma tumor nodules was proposed and would be expected to result in a maximal response[34].

Cisplatin

Cisplatin is an alkylating agent. It has been used by intraperitoneal administration for treating gastric cancer, ovarian cancer and diffuse malignant peritoneal mesothelioma[35]. Its molecular weight is 300 and the area under the curve ratio of intraperitoneal concentration to plasma concentration times time is approximately 10 (Figure 6). Although the area under the curve ratio is not as striking as some of the other intraperitoneal drugs, it can be used synchronously with many other agents. Its cytotoxicity is augmented by heat up to 3 times at 41.5℃[36]. It can effectively penetrate tumor nodules up to 3 mm. Currently, all patients with diffuse malignant peritoneal mesothelioma managed at our institution with cytoreductive surgery are given HIIC with doxorubicin and cisplatin.

Results of treatment with doxorubicin and cisplatin

The most recent update has shown that the median survival of 100 consecutive patients with diffuse malignant peritoneal mesothelioma was 50 mo and the 5-year survival rate was 44%. This survival statistic should be compared to historical controls with this disease who have a median survival of one year. In this study, all patients were given a combination of cisplatin plus doxorubicin. It is not possible to show the isolated effect of cisplatin in a majority of reports.

Melphalan

Melphalan is a well-known antineoplastic alkylating agent that has been used to treat cancer patients for over 50 years and it remains the most effective single drug used in heated limb perfusion for in-transit metastases from melanomas and advanced primary or recurrent extremity soft

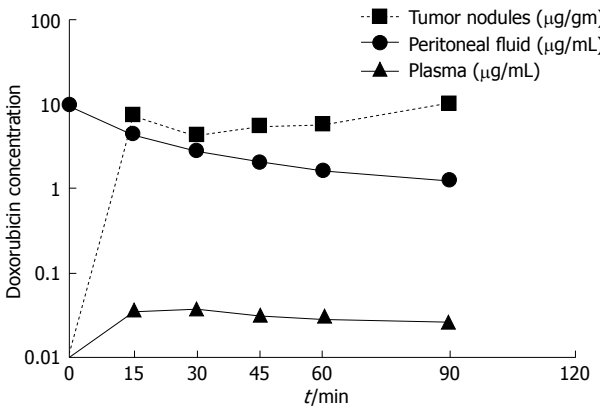

Figure 5 Pharmacokinetic profile of heated intraoperative intraperitoneal doxorubicin showing that the doxorubicin concentration in the tumor nodule is higher than that in the peritoneal fluid.

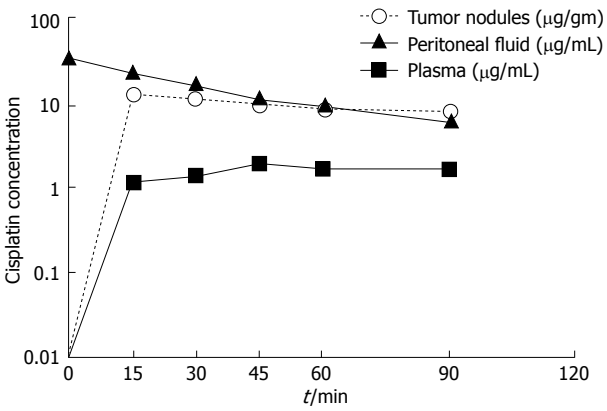

Figure 6 The area under the curve ratio of intraperitoneal concentration over plasma concentration times time of heated intraoperative intraperitoneal cisplatin is approximately 10.

tissue sarcomas[37-39]. Its molecular weight is 334 and the area under the curve ratio of intraperitoneal concentration to plasma concentration times time is approximately 93. It has remarkably increased pharmacological activity with heat in both *in vitro* and *in vivo* studies[22,40,41]. Glehen and colleagues showed that hyperthermia has little effect on intraperitoneal or plasma concentration of melphalan, and there was a significant increase in tissue penetration of this drug with heat[40]. Melphalan exerts its antineoplastic effect through the formation of interstrand DNA cross-links. It is believed that the formation of these DNA cross-links is promoted at increased temperatures, leading to enhanced cell killing. Recent phase I / II clinical trials using melphalan in patients with small volume residual carcinomatosis post cytoreductive surgery at a dose of 70 mg/m^2 have been completed at our institution.

Figure 7 shows the pharmacokinetic profile of melphalan given intraperitoneally at 70 mg/m^2 in 3 L of 1.5% dextrose peritoneal dialysis solution at 42℃ for 90 min. Pharmacokinetic studies showed that the drug concentration in the tumor nodules was approximately 30% of the intraperitoneal concentration and 10 times the plasma concentration[41].

EARLY POSTOPERATIVE INTRAPERITONEAL CHEMOTHERAPY

5-Fluorouracil

5-Fluorouracil is routinely used with EPIC for peritoneal carcinomatosis from numerous gastrointestinal malignancies. It is an antimetabolite that is incorporated into the DNA, which then causes chain termination. Its molecular weight is 130 and the area under the curve is 250. It is metabolized by a single pass through the liver, so that the systemic toxicity is very limited. Caution must be used in patients having liver dysfunction. When used as a single agent, the dose can be as high as 800 mg/m^2 per day for 5 d. When administered in patients after having had HIIC with mitomycin C, the dose is reduced to 650 mg/m^2[30]. Pestieau and colleagues demonstrated that the clearance of 5-FU from the peritoneal cavity could be significantly reduced with using hypertonic and high molecular weight carrier solutions[42]. This would, in turn, prolong 5-FU availability in the peritoneal cavity. It has also been reported that intraperitoneal 5-FU may play a role in preventing postoperative intraperitoneal adhesions and the clinical implications of this finding deserves more attention[43].

Paclitaxel

Paclitaxel is an antimitotic drug that stabilizes microtubules and inhibits their depolymerization for free tubulin. Its molecular weight is 862 and the area under the curve ratio is 1000. It can penetrate more than 80 cell layers and is extremely favorable for intraperitoneal use[44]. At our institution, EPIC with paclitaxel has been routinely used since 1998 for patients with diffuse malignant peritoneal mesothelioma. It is instilled as a lavage into the peritoneal cavity; gravity distribution is encouraged by the patient's movement from side to side for the first 6 h of the 23 h dwelling[33]. This treatment is repeated daily for the first 5 postoperative days. By the intention to treat principle, all patients are to receive EPIC with paclitaxel, unless they experience perioperative complications early in the postoperative period.

Mohamed and co-workers studied the use of 6% hetastarch as the carrier solution for paclitaxel. Because hetastarch is a larger molecule, its clearance from the peritoneal cavity was reduced, as compared to peritoneal dialysis solution. By maintaining an artificial ascites, hetastarch increased the exposure of peritoneal surfaces to paclitaxel; the volume of carrier solution was increased and the drug concentration remained unchanged (Figure 8)[45]. This is likely to further increase the tumor response to paclitaxel.

Stuart and colleagues recently found that the carcinogen diethylhexylphthalate (DEHP) is leached by a paclitaxel chemotherapy solution from polyvinyl chloride based containers. Because DEHP is present in all soft plastic tubing, precautionary steps must be taken or the carcinogen may be transferred to patients receiving intraperitoneal paclitaxel[46]. They recommended using non-DEHP containing plastic for paclitaxel delivery.

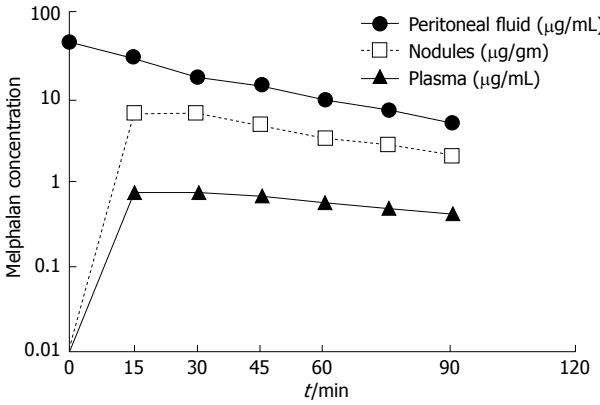

Figure 7 Pharmackinetics of HIIC with melphalan. Pharmacokinetic profile of melphalan given intraperitoneally at 70 mg/m^2 in 3 L of 1.5% dextrose peritoneal dialysis solution at 42℃ for 90 min. Pharmacokinetic studies showed that the drug concentration in the tumor nodules was approximately 30% of the intraperitoneal concentration and 10 times the plasma concentration.

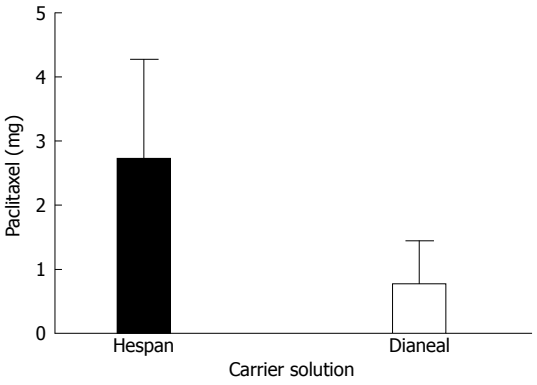

Figure 8 Mean total drug remaining in peritoneal cavity at 23 h. Hypertonic carrier solutions maintain the artificial ascites and paclitaxel concentrations, during early postoperative intraperitoneal paclitaxel instillation. Cite from reference[45].

FUTURE DIRECTIONS

Neoadjuvant intraperitoneal chemotherapy for gastric cancer

Recently, Yonemura and co-workers reported using combined systemic and intraperitoneal chemotherapy (bi-directional) for patients with gastric peritoneal carcinomatosis who were unable to have a complete cytoreduction due to the extensive nature of their disease[47]. Subsequently, they selected patients who responded to the neoadjuvant chemotherapy to undergo further cytoreductive surgery. The concept of this new approach, using neoadjuvant intraperitoneal chemotherapy to downstage those patients who are chemosensitive, is appealing. They reported that a complete cytoreduction was achieved in 25% of treated patients and this resulted in a prolonged survival.

As in many different peritoneal surface malignancies, completeness of cytoreduction was an important factor determining overall survival. It is related to the pretreatment tumor load, aggressiveness of the tumor and surgeon's technical ability. In patients with peritoneal dissemination involving the small bowel and small bowel mesenteric surfaces, it is almost impossible to remove all visible tumor nodules, and at the same time to preserve sufficient length of small bowel to ensure adequate nutrition. Neoadjuvant chemotherapy may have a useful role in this subgroup of patients to downstage the tumor load on the small bowel and its mesentery. Selecting those who responded to the intraperitoneal chemotherapy to undergo further cytoreduction may result in an improved overall survival.

Bi-directional intraoperative chemotherapy

Another use of bi-directional chemotherapy delivery has been proposed by Elias and colleagues. This involves the administration of intravenous chemotherapy simultaneous with HIIC[48]. The intravenous drug that is chosen is also augmented by heat and is delivered to the peritoneal tumor nodules through capillary flow. This is "hyperthermic targeting" of intravenous chemotherapy to the peritoneal surface. In this concept, tumor nodule penetration is not only from the surface by passive diffusion, but also from within by capillary flow. A study has been initiated to investigate HIIC of cisplatin and doxorubicin combined with intravenous ifosfamide after cytoreductive surgery for peritoneal dissemination of advanced or recurrent epithelial ovarian cancer and papillary serous carcinoma. It is hoped that this bi-directional hyperthermic local-regional treatment will result in improved survival of these patients. The agents most recommended for heat synergy are melphalan, ifosfamide and cyclophosphamide. These drugs may double their cytotoxicity for cancer cells when used with hyperthermia[36].

Adjuvant intraperitoneal chemotherapy

Surgery for gastrointestinal cancer is associated with an extremely high local recurrence rate. The mechanism whereby a large proportion of patients have disease recurrence confined to the resection site and peritoneal surfaces is related to traumatic dissemination of tumor emboli within the peritoneal cavity, and the implantation of these tumor emboli within the fibrinous exudates that accumulate at the resection site and on abraded peritoneal surfaces. Sources for these intraabdominal tumor emboli include coelomic perforation at the primary cancer site, severed lymphatic channels during surgery and disrupted tissue emboli within the blood loss from tumor specimen. Yu and co-workers reported an improved survival in patients who received adjuvant intraperitoneal chemotherapy for advanced gastric cancer[18,49]. It is likely that both HIIC and EPIC will benefit these patients with a high risk of intraperitoneal recurrence.

Standardization of treatment regimens for multi-institutional studies

Other drugs have been used for HIIC or EPIC by other groups around the world. Also, two chemotherapy agents have been approved by the FDA for intraperitoneal administration. These drugs are cyclophosphamide and nitrogen mustard. Currently, neither of these drugs are used regularly for treating patients with peritoneal surface

malignancy. A new drug that has been piloted in Villejuif by Elias and his colleagues is oxaliplatin[48]. Pharmacologic doses are used over a short time period in an attempt to increase drug penetration into the tumor. DeBree and colleagues have used docetaxel with heat[50]. Although docetaxel is not heat-augmented, it is possible that the hyperthermia will increase drug penetration into tumor nodules. Groups in Japan have used mitomycin C, cisplatin and etoposide, as a multi-drug chemotherapy solution[51]. Mitoxantrone has also been used by Link and colleagues in Wiesbaden in order to control debilitating ascites[52].

Although the rationale of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy is appealing, local-regional recurrence is common following this comprehensive treatment strategy. With new development and continuous evolution of treatment plans, reduced perioperative morbidity and mortality, along with increased disease-free survival and overall survival results are possible. A change in the management approach for patients with peritoneal surface malignancy is necessary. In contrast to the historical data, where the survival for patients with peritoneal dissemination was uniformly disappointing, survival has markedly improved with the new comprehensive treatments. It is necessary to form a multidisciplinary approach to assess patients with peritoneal surface malignancy. A medical oncologist should consult a surgeon in regard to the management of these patients before initiating a palliative approach with systemic chemotherapy. Systemic chemotherapy has been repetitively shown to be of no survival benefit. For future studies, many important issues, such as selection of drugs, potency of multiple agents, optimal degree of hyperthermia, concentration and duration of intraperitoneal chemotherapy, need to be clarified.

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BRIEF ARTICLE

Three novel *NEIL1* promoter polymorphisms in gastric cancer patients

Masanori Goto, Kazuya Shinmura, Hong Tao, Shoichiro Tsugane, Haruhiko Sugimura

Masanori Goto, Kazuya Shinmura, Hong Tao, Haruhiko Sugimura, First Department of Pathology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi Ward, Hamamatsu, Shizuoka 431-3192, Japan
Shoichiro Tsugane, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo 104-0045, Japan
Author contributions: Goto M performed the majority of the experiments; Shinmura K and Sugimura H designed the study and wrote the manuscript; Tao H performed the statistical analysis; Tsugane S coordinated the collection of all of the human materials and provided them.
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Correspondence to: Haruhiko Sugimura, PhD, First Department of Pathology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi Ward, Hamamatsu, Shizuoka 431-3192, Japan. hsugimur@hama-med.ac.jp
Telephone: +81-53-4352220 Fax: +81-53-4352225
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Abstract

AIM: To identify genetic polymorphisms in the promoter region of the human base excision repair gene *NEIL1* in gastric cancer patients.

METHODS: The *NEIL1* promoter region in DNA from 80 Japanese patients with gastric cancer was searched for genetic polymorphisms by polymerase chain reaction-single-strand conformation polymorphism and subsequent sequencing analyses.

RESULTS: Three novel genetic polymorphisms, i.e. c.-3769C>T, c.-3170T>G, and c.-2681TA[8], were identified in the *NEIL1* promoter region at an allele frequency of 0.6%, 9.4%, and 4.4%, respectively, in Japanese gastric cancer patients.

CONCLUSION: Three *NEIL1* promoter polymorphisms detected in this study may be of importance in gastric carcinogenesis.

Key words: Gastric cancer; *NEIL1*; Base excision repair; Genetic polymorphism

Peer reviewer: Tatsuo Kanda, MD, PhD, Division of Digestive and General Surgery, Graduate School of Medical and Dental Sciences, Niigata University, Niigata City 951-8510, Japan

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INTRODUCTION

Stomach tissue is exposed to oxidative stress, including inflammation induced by *Helicobacter pylori* infection, sodium chloride, and smoking[1-5]. Since severe oxidative stress leads to accumulation of huge amounts of damaged bases[6-9], maintenance of a system to repair damaged bases in the stomach is thought to be important. The base excision repair protein NEIL1 has activity that is capable of removing oxidatively damaged bases, including thymine glycol, 5-hydroxyuracil, urea, formamidopyrimidine-A, and formamidopyrimidine-G, which have been shown to cause mutagenesis and cell death[10-14]. We have recently demonstrated somatic inactivating *NEIL1* mutations and reduced NEIL1 expression in a subset of gastric cancers, suggesting that reduced NEIL1 activity is involved in gastric carcinogenesis[15]. In a recent investigation of the NEIL1 expression system

an approximately 1.2 kb sequence upstream of the transcriptional initiation site of the *NEIL1* gene was shown to have promoter activity by a luciferase reporter assay in human cells[16]. However, since no genetic polymorphisms have been reported in the promoter region thus far and genetic polymorphisms in the region may be of importance in gastric carcinogenesis, we tried searching DNA extracted from the blood of 80 gastric cancer patients for *NEIL1* promoter polymorphisms.

MATERIALS AND METHODS

Samples

Blood samples from 80 gastric cancer patients were obtained from hospitals in Nagano Prefecture, Japan, and genomic DNA was extracted from them with a DNA Extractor WB Kit (Wako, Osaka, Japan)[17]. The baseline characteristics of the patients have been described previously[17]. This study was approved by the Institutional Review Boards of Hamamatsu University School of Medicine and the National Cancer Center.

Polymerase chain reaction (PCR)-single-strand conformation polymorphism (SSCP) and sequencing analyses

PCR-SSCP analysis was used to examine the DNA samples for genetic polymorphisms in the *NEIL1* promoter region. An approximately 1.2 kb 5' upstream sequence that was shown to have promoter activity in a previous study[16] was divided into 8 regions (Figure 1A), and each region was amplified by PCR with HotStarTaq DNA polymerase (QIAGEN, Valencia, CA, USA). The primer sets used were: 5'-CAAATATTGCAGTCTGAAAGGGG-3' and 5'-GAAACTGATCAAGACAGGGGC-3' for region 1, 5'-GTTTTCTAATGCAGAGGTCTGG-3' and 5'-TACAGGGATAAGCCACTA CGC-3' for region 2, 5'-CCTCCTGATATGATGCAATTC-3' and 5'-CACTCCCAGCTGATTTTTG-3' for region 3, 5'-ATGGTGAAACCCCGTCTCTAC-3' and 5'-TGCTGGGAATTAGATCTAAAGGC-3' for region 4, 5'-AGCACCTAGGAAGTATCCCTG-3' and 5'-GTCTCAGCCAGTTGTTGTTTG-3' for region 5, 5'-CAAATTGAGAATGTGATGCAGC-3' and 5'-CAGATTTCCCCAATTGTCCC-3' for region 6, 5'-TGACCCATGATTGTAGCCTG-3' and 5'-GAGGTTTCGCCT TGTTGG-3' for region 7, and 5'-GAGGCGGGCAGATTACTTG-3' and 5'-CTCACTGCAGCC TCCACTTC-3' for region 8. The PCR products of regions 4 and 6 were digested with restriction enzymes *Mva*I (New England Biolabs, Beverly, MA, USA) and *Ava*I (New England Biolabs), respectively, in order to adjust their size to < 230 bp before SSCP. The PCR products of all regions were diluted with two volumes of loading solution, and after applying them to 8% polyacrylamide gels in the presence or absence of 5% glycerol, the products were electrophoresed at room temperature and 4℃ and detected by silver staining. PCR products exhibiting an abnormally shifted band in the SSCP analysis were directly sequenced with a BigDye Terminator Cycle Sequencing Reaction Kit (Applied Biosystems, Tokyo, Japan) and an ABI 3100 Genetic Analyzer (Applied Biosystems). A PCR product of region 7 was also sequenced after subcloning into a pGEM-T Easy vector (Promega, Madison, WI, USA). The reference nucleotide sequence is accession number NM_024608. Deviation of the genotype distribution from Hardy-Weinberg equilibrium (HWE) was tested by using SNPAlyze software (Dynacom, Yokohama, Japan).

RESULTS

We searched for genetic polymorphisms in the region containing *NEIL1* promoter activity by PCR-SSCP analysis using blood samples derived from 80 gastric cancer patients. Three genetic polymorphisms, c.-3769C>T, c.-3170T>G, and c.-2681TA[8], were identified in the *NEIL1* promoter region at an allele frequency of 0.6%, 9.4%, and 4.4%, respectively (Figure 1B). The distribution of the genotypes of these polymorphisms was in HWE. Examination of the frequency of the polymorphisms revealed a homozygote for the variant allele of only one of the three polymorphisms, c.-3170T>G, and in only one patient, indicating that the three polymorphisms in the *NEIL1* promoter are rare genetic polymorphisms.

DISCUSSION

In this study, we found three novel promoter polymorphisms, c.-3769C>T, c.-3170T>G, and c.-2681TA[8]. None of these polymorphisms has previously been reported or registered in the database of the single nucleotide polymorphism (dbSNP) homepage of the National Center for Biotechnology Information web site (web site : http://www.ncbi.nlm.nih.gov/SNP/) or the database of the Japanese single nucleotide polymorphism homepage (http://snp.ims.u-tokyo.ac.jp/), indicating that they are novel genetic polymorphisms.

Interestingly, when we used Genomatix software (http://www.genomatix.de/matinspector.html) to search for transcription factors that putatively bind to the sequence containing these polymorphism sites, a sequence containing c.-3170T was predicted to bind to GATA binding factors and a sequence containing c.-2681TA[7] was predicted to bind to a GZF1, a TATA-binding protein and LIM homeodomain factors. The change from c.-3170T to c.-3170G eliminates the binding site for GATA binding factors. On the other hand, although the change from c.-2681TA[7] to c.-2681TA[8] would appear to retain the sequence of binding sites for the GZF1, TATA-binding protein, and LIM homeodomain factors, there are examples of a change in the number of repetitive sequences in a promoter being associated with a difference in the expression level[18]. Thus, these nucleotide changes may be associated with a difference in the NEIL1 expression level. Moreover, since some factors involved in the regulation of the transcription level in human cells remain unknown,

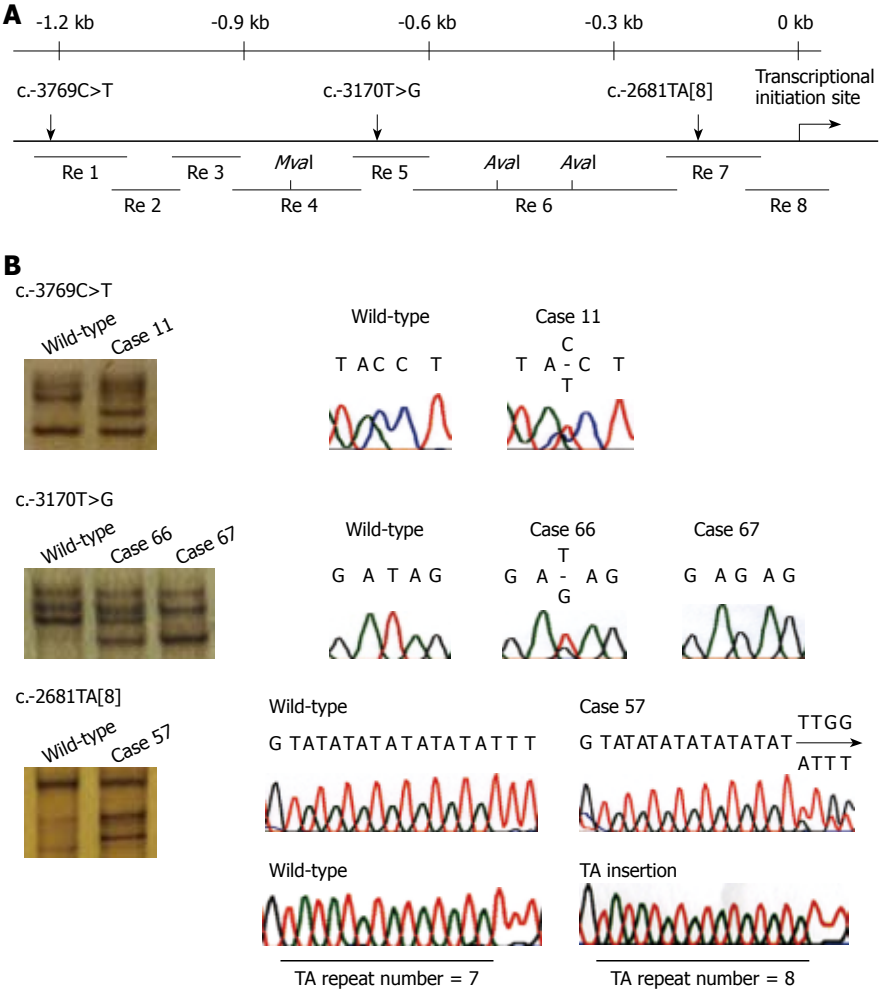

Figure 1 Identification of novel *NEIL1* promoter polymorphisms by PCR-SSCP and subsequent sequencing analyses. A: Schematic map of the *NEIL1* promoter region. The three genetic polymorphisms identified in this study are mapped, and the 8 PCR-amplified regions (Re 1-Re 8) and restriction enzyme sites are shown; B: Identification of c.-3769C>T, c.-3170T>G, and c.-2681TA[8] polymorphisms in the *NEIL1* promoter. The electropherograms on the left show the results of the sequencing analysis. The panels on the right show representative results of the PCR-SSCP analysis. Only the lowermost panels show the results of sequencing after subcloning the PCR product; the others show the results of direct sequencing.

the three *NEIL1* promoter polymorphisms may be associated with differences in the NEIL1 expression level by binding to factors that have yet to be identified.

Most common genetic polymorphisms have been registered in various genetic polymorphism databases, such as dbSNP. However, as shown in this study, there appear to be many genetic polymorphisms that still have not been registered in databases, the reason being that many unregistered genetic polymorphisms are rare. Since finding rare and novel polymorphisms requires many human samples and repeating this kind of study, the *NEIL1* data presented in this study are very valuable for future studies, such as searches for alleles that increase the risk of diseases and allele-specific expression analyses. Furthermore, NEIL1 protein plays a very important role in excision repair of oxidatively damaged bases, which have been implicated in a wide variety of human cancer. Promoter polymorphisms in some DNA repair genes, including *XRCC1, MLH1,* and *MSH2*, have recently been reported to be associated with an increased risk of cancer[19-21]. Like these examples, the novel *NEIL1* promoter polymorphisms identified by screening gastric cancer patients in this study may be associated with increased risk of gastric cancer. If so, this information should be of value in management to prevent the development of gastric cancer in individuals with the risk allele. We are therefore planning to examine the *NEIL1* promoter polymorphisms in the framework of a gastric cancer case-control study in the future, and we are also planning to investigate the effect of the polymorphisms on *NEIL1* promoter activity.

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COMMENTS

Background

The human base excision repair protein NEIL1 has activity that is capable of removing oxidatively damaged bases, such as thymine glycol and 5-hydroxyuracil. We have recently demonstrated somatic inactivating *NEIL1* mutations and reduced NEIL1 expression in a subset of gastric cancers, suggesting that reduced NEIL1 activity is involved in gastric carcinogenesis. In the present study, we searched for genetic polymorphisms in the promoter

region of the human *NEIL1* gene in gastric cancer patients and succeeded in identifying three novel genetic polymorphisms.

Research frontiers

Oxidized-DNA-base lesions have been implicated in carcinogenesis, and base excision repair proteins are involved in the repair of such lesions. The research frontier in the area of studying the relationship between the base excision repair genes and carcinogenesis lies in the discovery of genetic variants in the genes that are associated with increased cancer risk.

Innovations and breakthroughs

Stomach tissue is exposed to oxidative stress, including inflammation induced by *Helicobacter pylori* infection, sodium chloride, and smoking, and promoter polymorphisms in some DNA repair genes have been reported to be associated with increased cancer risk. However, there have been no reports of studies that have examined associations between *NEIL1* promoter polymorphisms and gastric cancer risk. The identification of three novel *NEIL1* promoter polymorphisms in this study should be of value for future research in this field.

Applications

The *NEIL1* data presented in this study will be useful for various future studies, such as studies that evaluate the effects of *NEIL1* polymorphisms on the risk of disease, haplotype analyses, and allele-specific expression analyses.

Peer review

This study investigated genetic polymorphisms in the human *NEIL1* gene and identified three polymorphisms in the promoter region of the gene. Although the study did not determine whether the polymorphisms are specific for gastric cancer patients, and no functional analysis of the polymorphisms was performed, the polymorphisms identified are indeed novel, and the results may facilitate future research in this field. In conclusion, the results of this study are somewhat valuable, and the paper appears to be worth publishing as a brief communication.

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CASE REPORT

Granular cell tumor of the pancreas: A case report and review of literature

Atsushi Kanno, Kennichi Satoh, Morihisa Hirota, Shin Hamada, Jun Umino, Hiromichi Itoh, Atsushi Masamune, Shinichi Egawa, Fuyuhiko Motoi, Michiaki Unno, Kazuyuki Ishida, Tooru Shimosegawa

Atsushi Kanno, Kennichi Satoh, Morihisa Hirota, Shin Hamada, Jun Umino, Hiromichi Itoh, Atsushi Masamune, Tooru Shimosegawa, Division of Gastroenterology, Tohoku University Graduate School of Medicine, 1-1, Seiryo-machi, Aobaku, Sendai City, Miyagi 980-8574, Japan
Shinichi Egawa, Fuyuhiko Motoi, Michiaki Unno, Department of Hepatobiliary-pancreatic surgery, Tohoku University Graduate School of Medicine, 1-1, Seiryo-machi, Aobaku, Sendai City, Miyagi 980-8574, Japan
Kazuyuki Ishida, Department of Pathology, Tohoku University Graduate School of Medicine, 1-1, Seiryo-machi, Aobaku, Sendai City, Miyagi 980-8574, Japan
Author contributions: Kanno A and Satoh K wrote the paper; Kanno A, Satoh K, Hirota M and Masamune A identified and diagnosed the patients; Egawa S, Motoi F and Unno M performed the operation; Ishida K confirmed the pathological diagnosis; Shimosegawa T supervised and participated in the editing the manuscript; All authors read and approved the final manuscript.
Correspondence to: Kennichi Satoh, MD, PhD, Division of Gastroenterology, Tohoku University Graduate School of Medicine, 1-1, Seiryo-machi, Aobaku, Sendai City, Miyagi 980-8574, Japan. ksatoh@mail.tains.tohoku.ac.jp
Telephone: +81-22-7177171 Fax: +81-22-7177177
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Abstract

Granular cell tumors, also called Abrikossof's tumors, were originally described by Abrikossof A in 1926. The first case of a pancreatic granular cell tumor was described in 1975 and only 6 cases have been reported. We describe a case of granular cell tumor in the pancreas showing pancreatic duct obstruction. Because imaging studies showed findings compatible with those of pancreatic carcinoma, the patient underwent distal pancreatectomy. Histological examination showed that the tumor consisted of a nested growth of large tumor cells with ample granular cytoplasm and small round nuclei. The tumor cells expressed S-100 protein and were stained with neuron-specific enolase and periodic acid-Schiff, but were negative for desmin, vimentin, and cytokeratin. The resected tumor was diagnosed as a granular cell tumor. To our knowledge, this is the seventh case of Granular cell tumor of the pancreas to be reported.

Key words: Granular cell tumor; Pancreas; Diagnosis; Distal pancreatectomy

Peer reviewers: Hao-Dong Xu, MD, PhD, Associate Professor, Department of Pathology and Laboratory Medicine, Aab Cardiovascular Research Institute, 601 Elmwood Ave. Box 626,Rochester, NY 14642, United States; Gary Y Yang, Associate Professor, Director, GI Radiation Medicine, Department of Radiation Medicine, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, United States.

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INTRODUCTION

Granular cell tumors (GCTs) are rare benign neoplasms of Schwann cell origin and have been found in virtually every location in the body, including breast[1], pituitary[2], central nervous system[3], respiratory tract[4], and gastrointestinal tract[5,6]. Supportive evidence that GCT arises from Schwann cells comes from the findings[7,8] that GCT cells contain S-100 protein, a unique acidic protein that is present in Schwann cells and satellite cells of ganglia but not often in nonneural soft tissue tumors. GCT of the pancreas is extremely rare and, to date, only 6 cases have been reported. We report an additional case of pancreatic

GCT and describe certain aspects of its clinical, radiologic, and histologic features.

CASE REPORT

A 39-year-old woman presented with mild unspecific abdominal pain for about 1 mo. In a local hospital, she initially had ultrasound of the abdomen, which identified a dilated main pancreatic duct from body to tail of the pancreas. She was referred to our hospital for evaluation of the pancreatic tumor. Twelve years previously, the patient underwent extraction of the left adrenal gland for primary aldosteronism. Otherwise, her past medical history was noncontributory. By conventional ultrasonography, the tumor was revealed as a hypoechoic area in the body of the pancreas. Endoscopic ultrasonography (EUS) showed a homogeneous solid mass with a regular border that appeared hypoechoic compared with the normal pancreatic parenchyma (Figure 1). Computed tomography (CT) demonstrated a 2 cm × 2 cm low-density lesion located in the body of the pancreas with dilatation of the main pancreatic duct. The early phase of dynamic CT revealed a slightly less enhanced mass in the pancreatic body compared to normal pancreatic tissues (Figure 2A). However, the tumor demonstrated gradual enhancement at the delayed phase of dynamic CT (Figure 2B). On magnetic resonance imaging (MRI), the tumor of the pancreas body was hypointense on a T1-weighted image (Figure 3A). In contrast, the peripheral and central areas of the tumor were, respectively, hypointense and hyperintense on aT2-weighted image (Figure 3B). The mass did not infiltrate the portal vein or celiac artery. The patient underwent endoscopic retrograde cholangiopancreatography, which showed a normal proximal pancreatic duct and a stricture in the midpancreatic duct with a dilated distal pancreatic duct (Figure 4). Cytological examination on material from the region of the narrowing was negative for malignant cells. Routine laboratory studies were normal. Carcinoembryonic antigen and cancer antigen 19-9 remained in the normal range. The preoperative differential diagnosis was pancreatic tumor including pancreatic adenocarcinoma. Laparotomy revealed that the tumor originated from the pancreatic body. There was no extension to adjacent organs, and no metastatic lesions were found. Distal pancreatectomy and splenectomy were performed. Histological examination confirmed that the tumor was completely resected. The margin was free of tumor cells, and none of 7 regional lymph nodes examined showed metastasis. The post-operative course was uneventful. Macroscopically, approximate 22mm × 20mm × 20 mm in diameter of whitish tumor was located in pancreatic body. The tumor encircled and narrowed the main pancreatic duct, and its upstream main pancreatic duct was dilated. Microscopic study showed a well-limited nodule made up of large clusters of benign cells with small nuclei and abundant granular cytoplasm (Figure 5A), which were weakly positive with the periodic acid-Schiff staining. S-100 protein staining was also positive in the cell cytoplasm by immunohistochemistry (Figure 5B). The final diagnosis was a granular cell tumor of the pancreas narrowing the main pancreatic duct.

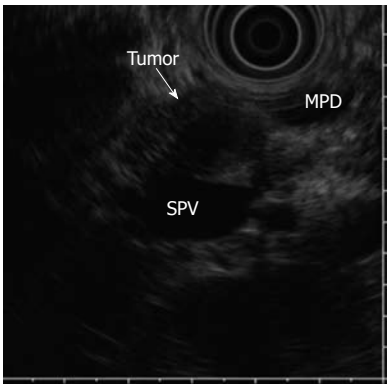

Figure 1 EUS image of pancreatic GCT. The tumor showed a homogeneous pattern and regular borders (arrow). EUS: Endoscopic ultrasonography; GCT: Granular cell tumor; MPD: main pancreatic duct; PV: portal vein.

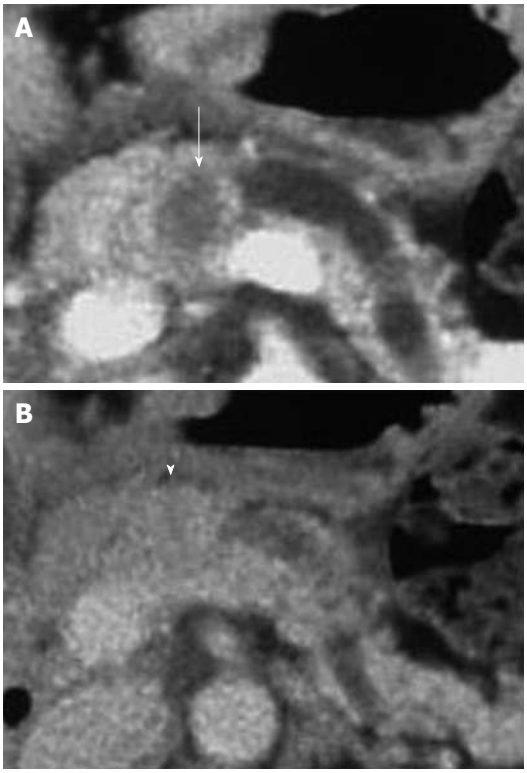

Figure 2 CT image of pancreatic GCT. A: CT showing poor enhancement of the tumor compared with that of the surrounding pancreatic parenchyma at early phase o dynamic CT (arrow); B: CT showing gradual enhancement of the tumor at delayed phase (arrowhead). CT: Computed tomography.

DISCUSSION

The first reported case of granular cell tumor was in 1926 by Abrikossoff[9]. The tumor was found in the skeletal muscle of the tongue. Although this type of tumor is known to arise in every part of the body, GCT of the pancreas is very rare. Only six cases of GCT of the pancreas had been reported[10-15] previously, and the characteristics of these cases are sumarized in Table 1. Because of the rarity of pancreatic GCT, the characteristic

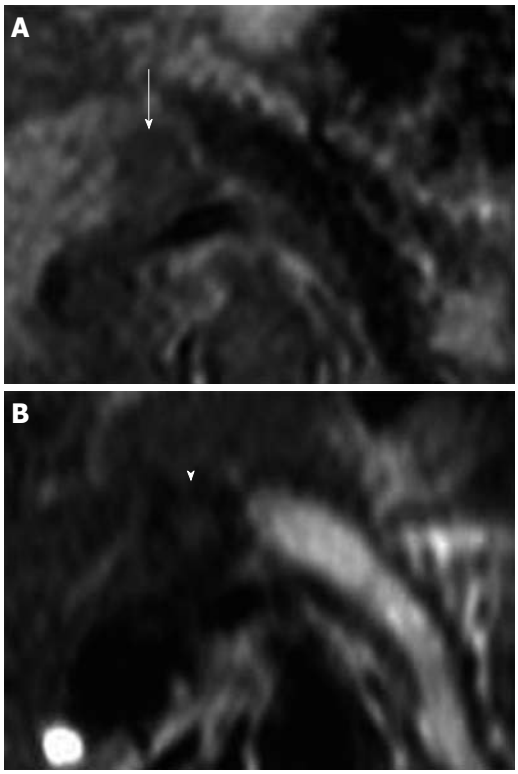

Figure 3 MRI findings of pancreatic GCT. A: The tumor showed a hypointense mass in the T1-weighted image (arrow); B: The surrounding and center of the tumor were hypointense and hyperintense on T2-weighted image, respectively (arrowhead). MRI: magnetic resonance imaging.

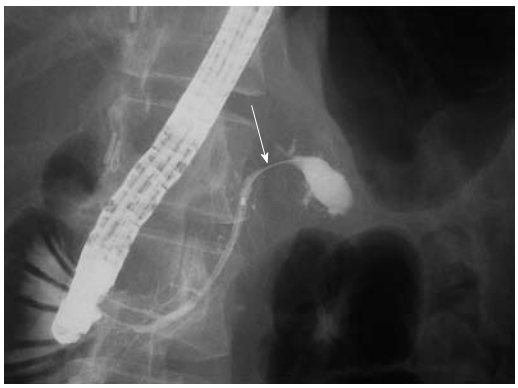

Figure 4 ERCP showing the stricture and the dilatation in the distal pancreatic duct (arrow). ERCP: Endoscopic retrograde cholangiopancreatography.

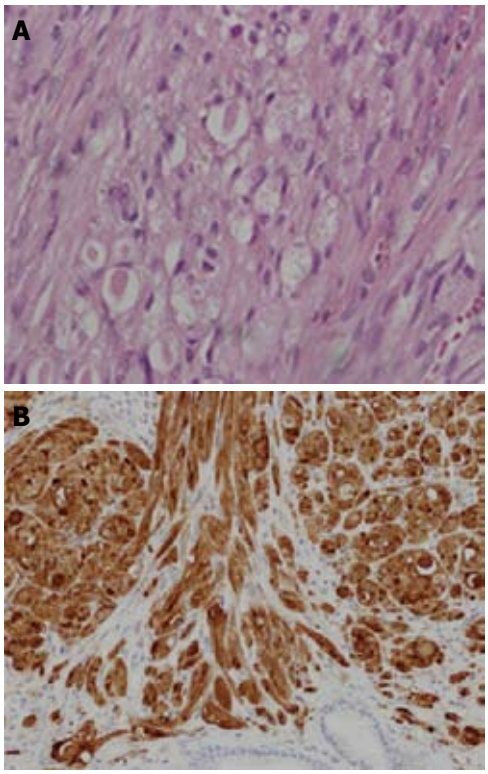

Figure 5 Histological findings. A: Microscopic study showed a well-limited nodule made of large clusters of benign cells with small nuclei and abundant granular cytoplasm; B: S-100 protein staining was positive in the cell cytoplasm.

epidemiology, clinical symptoms and radiological findings cannot be clarified. Although GCT is usually benign, malignant cases have been reported in subcutaneous leg tissue and esophagus (1%-2% of all GCT)[16]. There are reports of cases that have recurred or metastasized despite having a benign histological appearance. Although the morphology cannot reliably predict the biological behavior of GCT, local recurrence, rapid growth to a size greater than 4 cm, and an infiltrative pattern of growth should raise concerns about the possibility of malignancy[17-19].

Histopathologically, the present case of GCT showed diffuse oval tumor cells with low grade atypia and eosinophilic granules were found within the tumor cells. Positive PAS staining and immunohistochemical staining for S-100 protein and neuron specific enolase in the tumor provided the evidence for the diagnosis of GCT[20,21].

The preoperative diagnosis of pancreatic GCT is very difficult since, as mentioned, the characteristics of pancreatic GCT have not so far been clarified because this tumor is very rare. An accurate preoperative diagnosis of this tumor could not be made in all patients of pancreatic GCT. In 6 cases of pancreatic GCT, 3 patients had been misdiagnosed as having pancreatic cancer and resected surgically[12,13,15]. We also misdiagnosed this tumor as pancreatic cancer since it was seen as a low density mass in the pancreas which showed marked delayed enhancement during dynamic CT. In addition, ERCP demonstrated obstruction of the main pancreatic duct by the tumor. Though obstruction of the main pancreatic duct is one of the characteristics of malignant pancreatic tumors, this could not distinguish between malignant pancreatic tumors and pancreatic GCT since pancreatic GCT also exhibits obstruction of the main pancreatic duct[11-13]. There were, however, image findings distinct from those generally observed in pancreatic carcinoma. For example, the tumor showed a mass with a regular border by EUS and with different intensity between the peripheral and central area on the T2-weighted image of MRI. To our knowledge, there are no previous reports about the characteristics of MRI images of pancreatic GCT. In another organ, Kudawara described a GCT of the subcutis of the trunk showing as hypointense mass on T2-weighted

Table 1 Summary of the characteristics of the 6 cases of the granu;ar cell tumor of the pancreas found in the literature

Author	Age	Sex	Locarization	Size (mm)	Treatment
Wellman *et al*[10]	29	M	Head	6 × 4 × 3	-
Sekes *et al*[11]	31	F	Head	5	Pancreaticojejunostomy
Seidler *et al*[12]	62	F	Tail	7 × 5	Distal pancreatectomy
Bin-Sagheer *et al*[13]	50	F	Body-Tail	-	Distal pancreatectomy
Méklati *et al*[14]	26	F	Body-Tail	5	Distal pancreatectomy
Nojiri *et al*[15]	58	M	Head	13	Pancreatoduodenectomy
Present case	39	F	Body	20	Distal pancreatectomy

images since the tumor had abundant interstitial collagen fibers and a smaller amount of cellular components[22]. In contrast, Mukherji described GCT of the subglottic region appearing as heterogeneously increased signal intensity on T2-weighted images[23]. These findings of MRI in other organs were inconsistent with those of our case. Therefore, it is difficult to determine the characteristics of GCT since there are differences in the cellular density or surrounding area in every organ. Recently, it was reported that EUS- or CT-guided FNA is helpful for making the diagnosis of a pancreatic tumor[24,25]. However, FNA could not confirm the final diagnosis of GCT[14]. The final and exact diagnosis depends on the histopathological testing of the tissue specimen.

In conclusion, we experienced a case of pancreatic GCT with obstruction of the pancreatic duct. CT may be the best method to detect pancreatic GCT with respect to the location and size of the tumor, but accurate preoperative diagnosis remains very difficult. Although GCT is a rare disease, we should consider the possibility of GCT in the differential diagnosis of less enhanced tumors of the pancreas with pancreatic duct obstruction.

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Runjan Chetty, Professor, Department of Pathology and Gene Regulation, University of Glasgow, Western Infirmary (Pathology), Dumbarton Road, Glasgow, G11 6NT, Scotland, Unite Kingdom

Chris Deans, MD, FRCS, Department of Surgery, Edinburgh Royal Infirmary, 51 Little France Crescent, Edinburgh EH16 4SA, United Kingdom

Atsushi Imagawa, MD, Department of Gastroenterology, Tsuyama Central Hospital, 1756 Kawasaki Tsuyama-city, Okayama 708-0841, Japan

Tatsuo Kanda, MD, PhD, Division of Digestive and General Surgery, Graduate School of Medical and Dental Sciences, Niigata University, Niigata City 951-8510, Japan

Yukinori Kurokawa, MD, PhD, Department of Surgery, Osaka National Hospital, 2-1-14, Hoenzaka, Chuo-ku, Osaka 540-0006, Japan

Lars Mueller, MD, Department of General and Thoracic Surgery, University Hospital Schleswig-Holstein, Campus Kiel, Arnold-Heller-Str. 3, Kiel 24105, Germany

Marius Raica, Professor, Department of Histology and Cytology, "Victor Babes" University of Medicine and Pharmacy, Pta Eftimie Murgu 2, 300041, Timisoara, Romania

Antonio Russo, MD, PhD, Associate Professor, Genetic and Molecular Oncology Unit, Interdepartmental Center of Research in Clinical Oncology, School of Medicine, University of Palermo, Via del Vespro 127-90127 Palermo, Italy

Ondrej Slaby, PhD, Department of Comprehensive Cancer Care, Masaryk Memorial Cancer Insitute, Zluty kopec 7, 656 53 Brno, Czech

Hao-Dong Xu, MD, PhD, Associate Professor, Department of Pathology and Laboratory Medicine, Aab Cardiovascular Research Institute, 601 Elmwood Ave. Box 626, Rochester, NY 14642, United States

Yi-Zhuang Xu, PhD, Professor, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China

Siu Tsan Yuen, MBBS, MD, Department of Pathology, St. Paul's Hospital, 2 Eastern Hospital Road, Causeway Bay, Hong Kong, China

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Meetings

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http://www.gilearn.org/clinicalcongress

January 16-17, 2010
The Symposium on Clinical Interventional Oncology
Hollywood, Florida, United States

January 22-24, 2010
ASCO Gastrointestinal Cancers Symposium
Orlando, FL, United States

February 05-09, 2010
Cancer Genomics, Epigenomics & the Development of Novel Therapeutics
Waikoloa, HI, United States

February 19-20, 2010
8th International Symposium on the Evolution of Supportive Care in Oncology: the Era of Targeted Agents
New York, NY, United States

March 04-07, 2010
2010 Annual Meeting of the Society of Surgical Oncology
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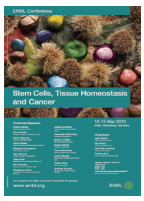
http://www.surgonc.org/

March 05-07, 2010
Genitourinary Cancers Symposium
San Francisco, CA, United States

March 07-11, 2010
16th International Conference on Cancer Nursing
Atlanta, GA, United States

March 25-28, 2010
20th Conference of the Asian Pacific Association for the Study of the Liver
Beijing, China
http://www.apasl2010beijing.org/en/index.aspx

April 17-21, 2010
101st Annual Meeting of the American Association for Cancer Research
Washington, DC, United States



May 12-15, 2010
Stem Cells, Tissue Homeostasis and Cancer
EMBL Heidelberg, Germany
http://www.embl.de/training/courses_conferences/conference/2010/STM10-01/

May 15, 2010
Digestive Disease Week 2010
American Association for the Study of Liver Diseases Ernest N. Morial Convention Center, 900 Convention Center Blvd, New Orleans, LA 70130, United States
http://www.ddw.org/

June 04-06, 2010
American Society of Clinical Oncologists Annual Meeting
Chicago, IL, United States

June 09-12, 2010
13th International Conference on Emergency Medicine
Singapore, Singapore

August 28-31, 2010
10th OESO World Congress on Diseases of the Oesophagus 2010
Boston, Massachusetts, United States

September 23-25, 2010
2010 Gastrointestinal Oncology Conference
The Sheraton Philadelphia City Center, Philadelphia, PA, United States
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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer

disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http//www.cdc.gov/ncidod/EID/eid.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and posi tioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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