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REVIEW

Treatment of Gastric Cancer With Peritoneal[Q2] Carcinomatosis by Cytoreductive Surgery and HIPEC: A Systematic Review of Survival, Mortality, and Morbidity

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Gastric cancer with peritoneal carcinomatosis has an extremely poor prognosis, which may be improved with cytoreductive surgery (CRS) combined with heated intraperitoneal chemotherapy (HIPEC). We systematically reviewed the literature regarding the efficacy of CRS + HIPEC in these patients. Electronic databases were searched from 2000 to 2010. Following CRS + HIPEC, overall median survival was 7.9 months and improved to 15 months for patients with completeness of cytoreduction scores of 0/1, however with a 30-day mortality rate of 4.8%.
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KEY WORDS: peritoneal carcinomatosis; gastric cancer; HIPEC; cytoreductive surgery

BACKGROUND

Description of the Condition

Gastric cancer is the fourth most common cancer worldwide and currently is the second leading cause of cancer-related mortality [1,2]. In addition to hematogenous spread, gastric cancer may disseminate along the inside surface of the peritoneal cavity leading to a condition known as peritoneal carcinomatosis (PC). In patients undergoing a potentially curative resection of gastric cancer, PC may be present in 5–20% [3]. Patients with PC of gastric origin have an extremely poor prognosis with a median survival estimated to be 1–3 months [4,5]. Systemic chemotherapy has been shown to improve median survival in metastatic gastric cancer to 7–10 months [5–7]; however the same improvement has not been reported in patients with gastric cancer and PC [8,9]. It is generally accepted that there is no role for surgery once the diagnosis of PC has been made in patients with gastric cancer.

Description of the Intervention

Since 1990, cytoreductive surgery (CRS) combined with heated intraperitoneal chemotherapy (HIPEC) has been used for the treatment of PC from gastrointestinal and ovarian malignancies [10,11]. The goal of CRS combined with HIPEC is to excise all macroscopic disease and treat the remainder of the peritoneal cavity with chemotherapy agents in order to improve the survival of these patients. CRS is accomplished by resecting the primary cancer and any other involved visceral organs and peritoneal surfaces. Upon completion of CRS, heated chemotherapy is perfused intraperitoneally for 60–90 min, allowing mixing and contact with tumor cells. By delivering the chemotherapy directly to the site of disease, a higher local concentration of the cytotoxic chemotherapy reaches residual microscopic tumor cells [12]. The combination of hyperthermia and chemotherapy has been shown to have a synergistic effect, thus augmenting the cytotoxicity of the chemotherapeutics [13]. Another advantage of localizing the chemotherapy within the peritoneum is that it minimizes undesirable systemic effects [12].

Why it Is Important to Do This Review

Patients with gastric cancer and PC have limited treatment options as PC has been shown to be less responsive to systemic chemotherapy [14]. CRS combined with HIPEC has been shown to drastically improve survival in patients with PC from colorectal cancer [15–17]. Both Mahteme et al. [15] and Glehen et al. [16] demonstrated a median survival of 32 months following CRS + HIPEC in patients with colorectal cancer compared to a median survival of 7 months with only supportive care [4]. Similarly, again in patients with colorectal cancer Elias et al. [18] demonstrated 5-year survival of 51% compared to 13% with palliative chemotherapy. However, whether CRS combined with HIPEC for advanced gastric cancer has any benefit is not clear.

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OBJECTIVES

To systematically review the literature regarding the effectiveness of CRS combined with HIPEC in patients with gastric cancer who also have PC.

METHODS

Criteria for Considering Studies for This Review

Types of studies. Human case-series (>5 cases), non-randomized controlled trials, randomized controlled trials, prospective cohort series.

Types of participants. The target population consists of adult (>18 years old) male or female patients with gastric cancer and PC. Patients were excluded if they had other sites of metastatic disease (e.g., liver, lung).

Types of interventions. The intervention under study was CRS (peritonectomy) combined with HIPEC. The primary gastric resection may be completed at the same surgery as the CRS or at a separate procedure.

Types of outcome measures. *Primary outcomes.* The primary outcome was overall survival following CRS combined with HIPEC. This included both median and mean survival or 1-, 2-, and 5-year survival rates.

Secondary outcomes.

1. Mortality.
2. Overall morbidity.
3. Type of morbidity.
4. Mean length of hospital stay (LOS).
5. Mean intensive care unit (ICU) stay.
6. Quality of life score.

Search Methods for Identification of Studies

Electronic searches. Published and/or English language studies were considered for review inclusion from 2000 to 2010. A comprehensive search of electronic databases (e.g., MEDLINE, EMBASE, SCOPUS, BIOSIS Previews, and the Cochrane Library) using broad search terms was completed (see Appendix for the search terms). The bibliographies of all included articles were examined to identify additional potentially relevant publications.

Data Collection and Analysis

Selection of studies. All studies involving CRS combined with HIPEC for adult patients with gastric cancer and PC were included. A trained librarian conducted the electronic searches, and one author (R.G.) conducted a prescreen to identify the articles clearly irrelevant articles by title, abstract, and keywords of publication. Following this, two independent reviewers (R.G. and D.A.) assessed the studies for relevance, inclusion, and methodological quality. Articles were classified as either:

1. Relevant (meeting all specified inclusion criteria).
2. Possibly relevant (meeting some but not all inclusion criteria).
3. Rejected (not relevant to the review).

Two reviewers (R.G. and D.A.) independently reviewed full text versions of all studies classified as relevant or possibly relevant. Disagreements were resolved by re-extraction, when necessary.

Data Extraction and Management

Two reviewers (R.G. and X.S.) independently extracted data from the full versions of the reviews. The extracted information included details of methods (e.g., randomization, blinding, etc.), demographics (e.g., age, sex, etc.), HIPEC characteristics (e.g., type of chemotherapeutic agent, temperature, etc.), clinical characteristics of each group, study inclusion and exclusion criteria, number of patients excluded and lost to follow up, details of intervention (e.g., CRS, peritonectomy, etc.), baseline and postintervention outcomes (e.g., median survival, cytoreductive completeness score, etc.), mortality/morbidity data (e.g., death, wound infections, abscess, hospital LOS, re-hospitalization, etc.), and methods of analysis.

Statistical Analysis

Analysis was performed on the data from included studies. Descriptive statistics (simple counts, means, medians) were used to report study, patient, and treatment-level data. The number of patients enrolled was used in the calculation of study and patient demographics. Efficacy outcomes of interest were synthesized by pooling data for patients that underwent CRS combined with HIPEC. Due to the high heterogeneity among the studies and lack of randomized controlled trials, a meta-analysis was not deemed appropriate. All calculations were performed using Stata 10 (StataCorp LP[Q3]) statistical software.

RESULTS

Results of the Search

A total of 144 articles were identified using our search criteria for screening (Fig. 1). Following assessment by our exclusion criteria, 66 were rejected and 78 studies remained for abstract review. Following abstract review, 43 studies were excluded and a total of 35 studies remained. A total of 10 primary studies meeting the inclusion criteria were identified following thorough assessment of the complete articles [19–28]. These included 1 non-randomized prospective controlled trial [22], 6 prospective case series [20,21,23,25,26,28], and 3 retrospective case series [19,24,27].

Included Studies

All 10 studies presented CRS combined with HIPEC outcome data on survival, mortality, or morbidity. Baseline characteristics of patients in the included studies are provided in Table I. A total of 441 patients were assessed in the 10 studies and numbers of patients in each study ranged between 7 and 159. The average age of the patients was 48.5 years, ranging from 48 to 55. The patients had a median follow-up of 46 months (range: 19–74 months).

Survival

The primary outcome of survival was assessed as median survival and 1-, 2-, 5-year survival (Table II). Overall median survival was 7.9 months (range: 6.1–9.2 months) based on five included studies [19,21,22,24,25] and 15 months (range: 9.5–43.4 months) for patients with completeness of cytoreduction (CC) scores of 0 or 1 from four studies [19,21,22,25]. Seven included studies reported 1-year survival following CRS combined with HIPEC of 43% (range: 22–68%) [19,21,24–28]. Two studies reported 5-year survival of 13% for the gastric cancer + PC patients [19,26].

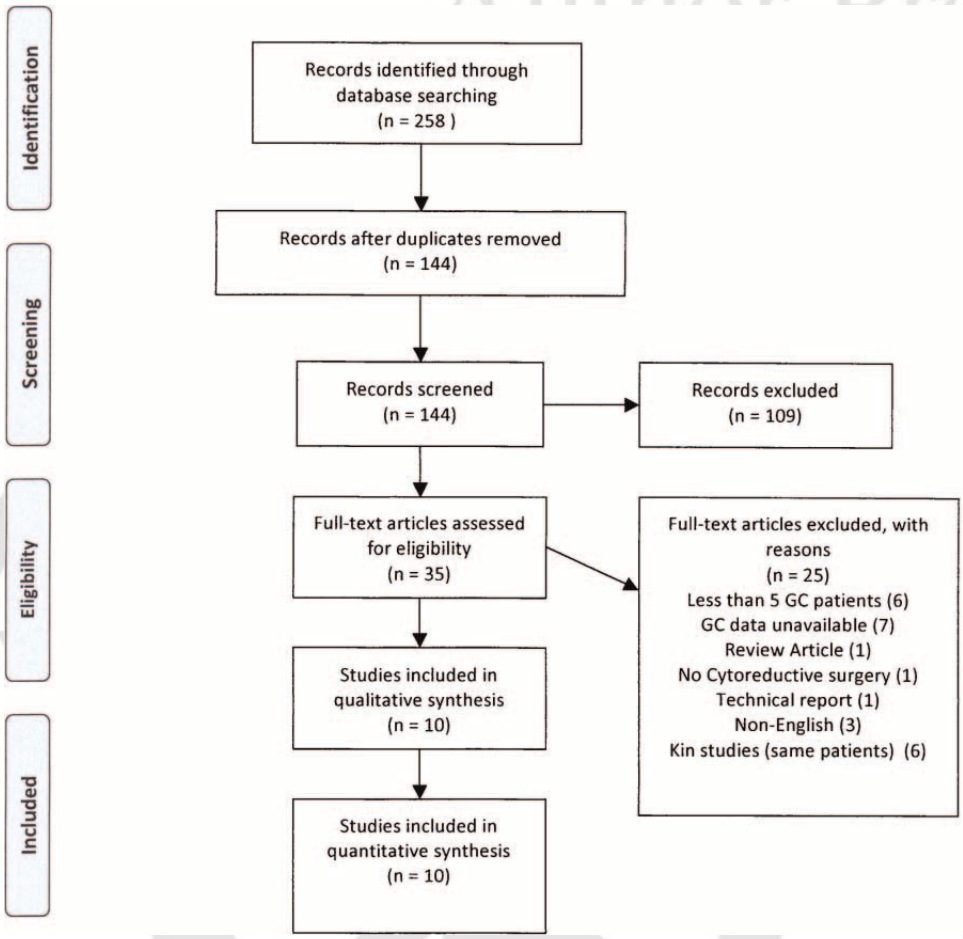

Fig. 1. Flow chart showing systematic review search results.

Characteristics of CRS Combined With HIPEC

Details of HIPEC are provided in Table III. Both open and closed HIPEC technique was utilized in the included studies. The most common chemotherapeutic agents were cisplatin and mitomycin, with intra-abdominal temperatures typically between 40 and 44°C. The duration of HIPEC was between 30 and 120 min.

Mortality and Morbidity Outcomes

Nine included studies reported a total of 19 treatment-related deaths from a total of 467 patients, an overall mortality rate of 4.8% (Table IV). Overall morbidity was reported by 8 included studies at 21.5% (Table V). The most common complications following CRS combined with HIPEC were abscess, fistula, and anastomotic leak (Table V).

TABLE I. Baseline Characteristics Within Included Studies for Systematic Review

Refs.	Country	Study design	No. of patients	Age (years)	Gender (% male)	Dx	Length of follow-up (months)
Glehen et al. [19]	France	Retrospective case series multicenter	159	53.4[a]	52.2	GC + PC	20
Yang et al. [20]	China	Prospective case series	21	50	53.6	GC + PC	22
Shen et al. [21]	USA	Prospective case series	43	53[a]	N/A	GC + PC	55
Scaringi et al. [22]	France	Prospective controlled study	26	53.7[a]	73	GC + PC	N/A
Roviello et al. [23]	Italy	Prospective case series	12	55[a]	27.1	GC + PC	19
Farma et al. [24]	USA	Retrospective case series	9	48	33.3	GC + PC	74
Yonemura et al. [25]	Japan	Prospective case series	107	52[a]	45.8	GC + PC	46
Mussa et al. [26]	Italy	Prospective case series	7	52	N/A	GC + PC	N/A
Fujimura et al. [27]	Japan	Retrospective case series	15	49.7[a]	46.7	GC + PC	36
Beaujard et al. [28]	France	Prospective case series	42	51[a]	56.6	GC + PC	74
Total/*median*			441	48.5[a]			*46*

Dx, diagnosis; GC, gastric cancer; PC, peritoneal carcinomatosis; N/A, not available.
[a]Mean.

TABLE II. Survival Following CRS + HIPEC for Gastric Carcinoma With PC

Refs.	Median survival (months)	Survival with CCR 0/1 (months)	1-Year survival (%)	2-Year survival (%)	5-Year survival (%)
Glehen et al. [19]	9.2	15	43		13
Yang et al. [20]		43.4	50	42.8	
Shen et al. [21]	6.1				
Scaringi et al. [22]	6.6	15			
Roviello et al. [23]					
Farma et al. [24]	8		22.2	11.1	
Yonemura et al. [25]	11.5	19.2	35.5	13.1	
Mussa et al. [26]			68	50	13
Fujimura et al. [27]			57	21	
Beaujard et al. [28]			48	33	
Range	6.1–9.2	9.5–43.4	22–68	11–50	
Median	7.9	15	43	18	13

CCR, completeness of cytoreduction score 0/1; LOS, length of stay; ICU, intensive care unit.

DISCUSSION

CRS combined with HIPEC may improve survival in select patients with gastric cancer with PC. Median survival is increased to 15 months in patients where CC can be achieved compared to 3 months with only basic supportive therapy. Gastric cancer with PC is typically treated with systemic chemotherapy, however the efficacy is difficult to determine based on the literature. Systemic chemotherapy has been shown to improve median survival in metastatic gastric cancer to 7–10 months by three clinical trials, however the patient populations were heterogeneous with inconsistent randomization, with the majority of patients having no PC [5–7]. Similarly, Preusser et al. [14] also report decreased response rates to systemic chemotherapy in patients with PC. No clinical trials have directly compared CRS combined with HIPEC versus systemic chemotherapy in patients with gastric cancer and PC. Two recent studies have reported median survival times of greater than 15 months in patients with gastric cancer with PC who were treated with CRS combined with HIPEC [19,25]. Importantly, both of these studies also reported the CC as an independent prognostic factor for survival.

Much of the initial work using CRS combined with HIPEC comes from the application of this treatment in patients with primary peritoneal malignancy such as pseudomyxoma peritonei [29]. CRS is used primarily to treat gross and macroscopic disease as experimental studies suggest that local chemotherapy may penetrate to a maximal depth of 3 mm [30]. Additionally, CRS also removes intra-abdominal adhesions allowing greater distribution of cytotoxic agents [31]. HIPEC is subsequently administered to target residual microscopic intra-abdominal disease. Hyperthermia has two potential benefits; first, hyperthermia may induce apoptosis, denature proteins and impair DNA repair [32]. Second, hyperthermia allows for greater drug accumulation within tumor nodules [33,34]. Pseudomyxoma however is a much more indolent disease process than gastrointestinal adenocarcinoma.

Despite the paucity of evidence to support systemic chemotherapy for PC, it is often given to patients with GC and PC. It is postulated that the ineffectiveness of systemic chemotherapy for PC is related to the presence of a blood-peritoneal barrier [35]. However, the use of neoadjuvant chemotherapy has been reported to reduce the burden of macroscopic PC [36,37]. Yano et al. [37] reported disappearance of PC following chemotherapy in 3 of 33 patients. Inokuchi et al. [38] reported partial response in 9 of 13 patients (69%) following chemotherapy for PC of gastric origin. Neoadjuvant therapy for PC has progressed further to bidirectional induction chemotherapy termed ''neoadjuvant intraperitoneal/systemic chemotherapy'' (NIPS). NIPS involves the combination of systemic chemotherapy and intermittent intraperitoneal chemotherapy. Yonemura et al. [39] reported that 63% of patients with positive cytology from peritoneal washings had negative cytology following NIPS. They also reported improved survival in those patients with negative cytology following NIPS. Unfortunately, none of the included trials in this systematic review reported the use of NIPS or neoadjuvant chemotherapy in their protocols.

An important consideration for GC is the timing of PC, specifically the presence of synchronous PC during the initial diagnosis versus metachronous development of PC following initial treatment of GC. Only two of the included studies [22,23] reported the presence of synchronous and metachronous PC, however we were unable to isolate this from the extracted data. It may be speculated that metachronous PC may represent progression of disease, however this remains controversial. Because PC is usually not visible via standard imaging (i.e., computed tomography), it may be more difficult to diagnose metachronous disease while it is still considered resectable. For this reason some surgeons may consider synchronous PC more treatable than metachronous PC. Further research may clarify the optimal approach to synchronous and metachronous PC of gastric origin.

In patients with colorectal cancer with PC, multiple phase II trials have combined CRS with HIPEC as primary treatment [15,17,18]. Median survival was estimated between 18 and 60 months for

TABLE III. Hyperthermic Intraperitoneal Chemotherapy Regimen in Included Studies

Refs.	HIPEC technique	Duration of HIPEC (min)	Intra-abdominal temperature (°C)	Drug regimen
Glehen et al. [19]	Open/closed	30–120	40–43	MMC, CDDP or OXIRI, 5-FU
Yang et al. [20]	Open	90–120	43	Hydroxycamptochecin or CDDP, MMC
Shen et al. [21]	Closed	120	40–42.5	MMC
Scaringi et al. [22]	Open	60–90	41–43	MMC, CDDP
Roviello et al. [23]	Closed	60	41–43	CDDP, MMC
Farma et al. [24]	Closed	90	N/A	CDDP, PT
Yonemura et al. [25]	Open	60	42–43	MMC, CDDP, ETP
Mussa et al. [26]	Open/closed	60	42–43	MMC
Fujimura et al. [27]	N/A	60	42–43	CDDP, MMC, ETP
Beaujard et al. [28]	Closed	90	36–43	MMC

CDDP, cisplatin; MMC, mitomycin; PT, paclitaxel; ETP, etoposide; OX, oxaliplantin; IRI, irinotecan; 5-FU, flourouracil; N/A, not available.

TABLE IV. Mortality and Hospital Length of Stay of CRS Combined With HIPEC

Refs.	Treatment-related deaths	Mortality (%)	Cause of death	Hospital LOS (days)	ICU stay (days)
Glehen et al. [19]	11	6.5	NL		
Yang et al. [20]	3	10.7	2 Ileus,1 ARDS, 1 pneumonia		1–3
Shen et al. [21]		4		15	2
Scaringi et al. [22]	1	11	Septic shock	16	
Roviello et al. [23]	1	1.6	MOF	7	
Farma et al. [24]	1	5.6	CVA		
Yonemura et al. [25]	3	7	1 ARF, 1 A-leak, 1 bleeding		
Mussa et al. [26]	1	14.3			
Fujimura et al. [27]	0	0			
Beaujard et al. [28]	3	3.60	1 PE, 1 MOF, 1 Septic shock	11	
Total/*median*	19	*4.8* (0–14.3)			

MOF, multiple organ failure; CVA, cerebrovascular accident; PE, pulmonary embolism; ARDS, adult respiratory distress syndrome; ARF, acute renal failure; A-leak, intestinal anastomosis leak; NL, not listed.

patients treated with CRS and HIPEC [18,40,41]. However, the improved survival seen in patients with colorectal cancer and PC with CRS combined with HIPEC raised concerns regarding potential selection bias. Verwaal et al. [42] published a randomized trial comparing systemic chemotherapy to CRS combined with HIPEC followed by systemic chemotherapy for PC of colorectal origin and demonstrated a survival benefit. In this study, 105 patients were randomized to receive systemic chemotherapy (controls) versus CRS combined with HIPEC followed by systemic chemotherapy (treatment group). The median survival was 22.3 months in the treatment group, which was significantly greater than survival of the controls (12.6 months) by 10 months [42]. A follow-up of this trial with 8-year follow-up of the same patients, further confirmed a survival benefit in patients treated with CRS and HIPEC [43]. A meta-analysis of CRS and HIPEC also reported improved survival [44]. PC of gastric origin treated with CRS combined with HIPEC has demonstrated improved survival in the literature when CC is performed. Elias et al. [18] report the highest median survival for patients with CC0 of 60 months, however these results have not been repeated in a randomized controlled trial.

CRS combined with HIPEC has been perceived as a highly morbid procedure regardless of the origins of the PC. Our review revealed a mortality of 4.8% and morbidity of 21.5%. A recent review of CRS and HIPEC for the treatment of PC of any origin reported a mean mortality rate of 2.9%, with tertiary centers reporting a mortality rate ranging from 0.9% to 5.8% [45]. Combined major morbidity was reported to be 28.8% with fistula, abscess, and ileus being most common [44]. CRS combined with HIPEC for gastric cancer with PC has comparatively similar mortality and morbidity rates as PC of other organ origins. Since gastric cancer + PC is essentially a fatal disease with conventional treatment options, these mortality and morbidity rates may be acceptable to patients. In PC of colorectal origin, careful patient selection and increased center experience seem to be the basis for improving survival and minimizing complications [46]. The importance of achieving CC is highlighted by this review, with doubling of the median survival with a CC score of 0 or 1. This suggests that CRS and HIPEC for GC + PC should only be considered in select patients if the surgeon is very confident that a CC0 is possible.

The experience of the institutions and surgeons performing CRS and HIPEC has been shown to be associated not only with survival, but also with both mortality and morbidity. The multi-institutional study by Glehen et al. [19], which included 159 patients from 15 institutions, reported that the institution where CRS and HIPEC was performed, was an independent prognostic factor of postoperative complications. CRS and HIPEC are considered technically challenging procedures with steep learning curves [47]. Smeenk et al. [48] performed CRS and HIPEC over a 10-year period for PC and analyzed rate of CC and postoperative morbidity over three consecutive treatment periods. They reported a significantly increased rate of CC from 35.6% to 65.1% and decreased postoperative morbidity from 71.2% to 34.1%. Furthermore, they reported that the peak of the learning curve was reached after 130 procedures. Yan et al. [49] compared morbidity rates following CRS and HIPEC for peritoneal

TABLE V. Morbidity of CRS Combined With HIPEC for Gastric Carcinoma + PC

Refs.	Overall morbidity (%)	Re-operation (%)	Sepsis	Fistula	Abscess	Hematologic toxicity	Ileus	Anastomotic leak
Glehen et al. [19]								
Yang et al. [20]	14.3		1		1		2	1
Shen et al. [21]	43							
Scaringi et al. [22]	27			9	5	2		
Roviello et al. [23]	27.9	8.2		5	2	5	1	
Farma et al. [24]	55.6				1	3		
Yonemura et al. [25]	21.5			1	6			6
Mussa et al. [26]			1					
Fujimura et al. [27]	50	33.3			2			
Beaujard et al. [28]	9.6	4.8				3	2	1
Total/*median*	*21.5*		2	10	11	2	2	7

surface malignancies in 140 consecutive patients. They reported that severe morbidity rates decreased from 30% to 10% when comparing the last 70 cases with the first 70 cases. Though the independent factors predicting adequate learning of CRS and HIPEC remain controversial, increasing experience of an institution may be associated with a learning curve, which might lead to improved surgical decision-making and patient selection.

Controversy remains regarding the treatment of gastric cancer patients with PC. Our systematic review demonstrates similar mortality and morbidity rates for CRS and HIPEC for gastric cancer with PC compared to treatments of PC from other organs. Survival is improved in these patients compared to basic supportive therapy, however systemic chemotherapy data specifically for this population is sparse [4,5]. Heterogeneity among the included studies in terms of HIPEC technique, duration, and cytotoxic drug regimen limit a clear recommendation. However, evidence presented here, based on available literature, suggests a role for CRS and HIPEC in this patient population. As previously suggested [20], phase III prospective randomized controlled trials are needed to delineate the role of CRS and HIPEC treatment strategy for patients with gastric cancer and PC. Currently the GYMSSA trial is being conducted to compare gastrectomy with metastasectomy plus systemic chemotherapy (GYMS) to systemic chemotherapy alone (SA) in patients with GC [50]. As a prospective phase III randomized trial, GYMSSA has the potential to clarify whether an aggressive surgical approach combined with HIPEC and systemic chemotherapy may benefit GC patients. However, the patient population that the GYMSSA trial has included differs from the patients included in our systematic review. The GYMSSA trial includes limited metastatic disease including lung and liver metastases, while our review focuses on GC with PC, without evidence of distant metastases. The GYMSSA trial [50], expects to recruit up to 140 patients, and it may be possible upon completion of the trial to perform subgroup analysis for survival of GC patients with only PC. However, with current evidence, we can only conclude that CRS combined with HIPEC may be efficacious in patients with PC from GC when CC is achievable. It is possible that with careful patient selection and increasing experience in specialized centers, CRS and HIPEC may eventually become an accepted treatment strategy for select patients presenting with GC + PC.

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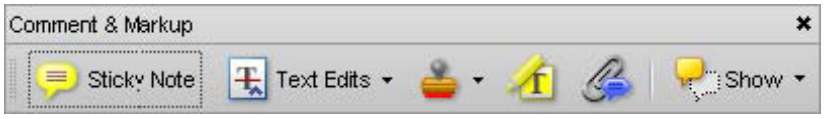

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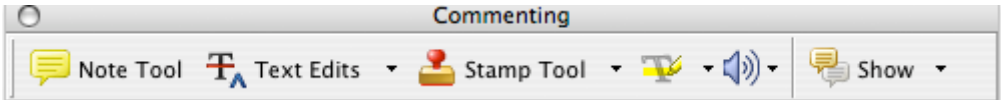

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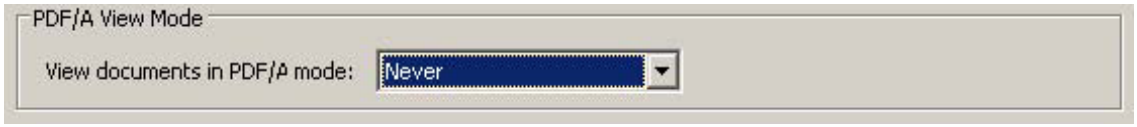

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