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REVIEW

Treatments and overall survival in patients with Krukenberg tumor

Ruggero Lionetti[1] · Marcello De Luca[1] · Antonio Travaglino[2] · Antonio Raffone[3] · Luigi Insabato[2] · Gabriele Saccone[3] · Massimo Mascolo[2] · Maria D'armiento[4] · Fulvio Zullo[3] · Francesco Corcione[1]

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Abstract

Background Krukenberg tumor (KT) is a rare secondary ovarian tumor, primarily localized at the gastrointestinal tract in most cases. KT is related to severe prognosis due to its aggressiveness, diagnostic difficulties and poor treatment efficacy. Several treatments have been used, such as cytoreductive surgery (CRS), adjuvant chemotherapy (CT) and/or hyperthermic intraperitoneal chemotherapy (HIPEC). To date, it is still unclear which treatment or combination of treatments is related to better survival.

Objective To assess the most effective therapeutic protocol in terms of overall survival (OS).

Methods A systematic review of the literature was performed by searching MEDLINE, Scopus, EMBASE, ClinicalTrial.gov, OVID, Web of Sciences, Cochrane Library, and Google Scholar for all studies assessing the association of treatments with OS in KTs. The effectiveness of each treatment protocol was evaluated by comparing the OS between patients treated with different treatment protocols.

Results Twenty retrospective studies, with a total sample size of 1533 KTs, were included in the systematic review. Therapeutic protocols used were CRS in 18 studies, CT in 13 studies, HIPEC in 7 studies, neoadjuvant CT in 2 studies, and some combinations of these in 6 studies. Seven studies showed that CRS significantly improved OS compared to other treatments or association of treatments without it. 11 studies showed that CRS without residual (R0 CRS) had a significantly better OS than CRS with residual (R + CRS). Five studies showed that CT significantly improved OS, but other five showed it did not. Two studies showed that HIPEC in association with CRS improved OS, while another study showed that efficacy of HIPEC was comparable to CT. Two studies evaluated neoadjuvant CT, but results were conflicting.

Conclusion CRS and in particular R0 CRS are the treatments showing the clearest results in improving OS in KT patients. Results about CT are conflicting. HIPEC appears effective both alone and in combination with CRS, and also related to fewer adverse effect than CT. The usefulness of neoadjuvant CT is still unclear. The association of R0 CRS with HIPEC seems to be the most effective and safe therapeutic protocol for KT patients.

Keywords Cancer · Metastasis · Prognosis · Management · oncology · hazard ratio · Therapy

Introduction

Krukenberg tumor (KT) is a rare secondary ovarian tumor that represents 1–2% of all ovarian tumors.

The most frequent primary localization is the gastrointestinal tract, while breast and appendix are involved in a minor percentage of cases [1, 2].

Not all secondary tumors of the ovary are KT: signet ring cells that produce mucin and the sarcomatoid proliferation of the stroma are the distinguishing features [3].

KT has a poor prognosis due to its aggressiveness, advanced stage, diagnostic difficulties and poor treatment efficacy [2, 4].

✉ Antonio Travaglino
antonio.travaglino.ap@gmail.com

1 General Surgery Unit, Department of Public Health, School of Medicine, University of Naples Federico II, Naples, Italy

2 Anatomic Pathology Unit, Department of Advanced Biomedical Sciences, School of Medicine, University of Naples Federico II, Via Sergio Pansini, 5, 80131 Naples, Italy

3 Gynecology and Obstetrics Unit, Department of Neurosciences, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy

4 Pathology Unit, Department of Public Health, School of Medicine, University of Naples Federico II, Naples, Italy

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Available treatments consist of cytoreductive surgery (CRS), adjuvant chemotherapy (CT) and/or hyperthermic intraperitoneal chemotherapy (HIPEC), but there is no clarity about which treatment or combination of treatments is related to better survival [5–7].

The aim of this study was to assess which treatment or combination of treatments may be the most effective in terms of increased overall survival (OS) in patients with KT.

Materials and methods

Methods for electronic search, study selection, risk of bias assessment and data extraction were defined before the beginning of the study.

All stages of the review were conducted independently by three reviewers (RL, MDL, AR). Disagreements were resolved by consensus among the three reviewers, or among all authors if necessary.

The study was reported according to the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [8].

Search strategy

MEDLINE, Scopus, EMBASE, ClinicalTrial.gov, OVID, Web of Sciences, Cochrane Library, and Google Scholar were used as electronic databases to be searched. Relevant articles were searched from the inception of each database to August 2018. Several searches were performed using combinations of the following text words: "krukenberg"; "ovarian"; "ovary"; "ovaries"; "metastasis"; "metastases"; "metastatic"; "tumor"; "cancer"; "neoplasm"; "survival". Reference from relevant studies were also assessed.

Study selection

All retrospective or prospective studies assessing the association of treatments with OS in KTs were included.

Exclusion criteria, defined a priori, were sample size < 10; case reports; reviews. No language restrictions were applied.

Risk of bias within studies assessment

According to the Methodological Index for Non-Randomized Studies (MINORS) [9], we evaluated the risk of bias for each study, in relation to seven domains: (1) Aim (i.e. clearly stated aim); (2) Patients (i.e. all patients satisfying the criteria for inclusion were included in the study during the study period); (3) Data (i.e. data were collected according to a protocol established before the beginning of the study); (4) Endpoint (i.e. unambiguous explanation of the criteria used to measure outcomes); (5) Bias (i.e. the study endpoint was assessed without bias); (6) Follow-up (i.e. the follow-up was sufficiently long to allow the assessment of the main endpoint), (7) Loss (i.e. no more than 5% of patients were lost to follow-up).

The risk of bias was categorized as "low" (criterion met), "high" (criterion not met) or "unclear" (data not reported).

Data extraction and analysis

Data from original studies were not modified during extraction

Primary extracted data were therapeutic protocols used to treat KTs with the related OS. Secondary extracted data were country, period of recruitment, sample size, patients' age, primary site of the tumor, treatment side effects.

The effectiveness of each treatment protocol was evaluated by comparing the OS between patients treated with different treatment protocols.

The data analysis was performed using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014).

Results

Selection and characteristics of the included studies

Twenty retrospective studies, with a total sample size of 1533 KTs, were included in the systematic review. The whole process of study selection is reported in detail in Fig. 1.

Therapeutic protocols used were CRS in 18 studies, CT in 13 studies, HIPEC in 7 studies, neoadjuvant CT in 2 studies, and combinations of these in 6 studies.

Characteristics of the included studies, patients and KTs were shown in Table 1.

Risk of bias within studies assessment

About the "Aim", "Data" and "Endpoints" domains, all studies were classified at low risk of bias.

About the "Patients" domain, three studies were categorized at low risk of bias [10–12], while 15 at unclear risk of bias because they did not clearly specify the inclusion criteria [4–7, 13–23]. Last, two studies were classified at high risk of bias: one for considering all metastatic ovarian tumors as KTs irrespectively of histology [24], and another one for lumping together KT and other metastatic ovarian cancers [25].

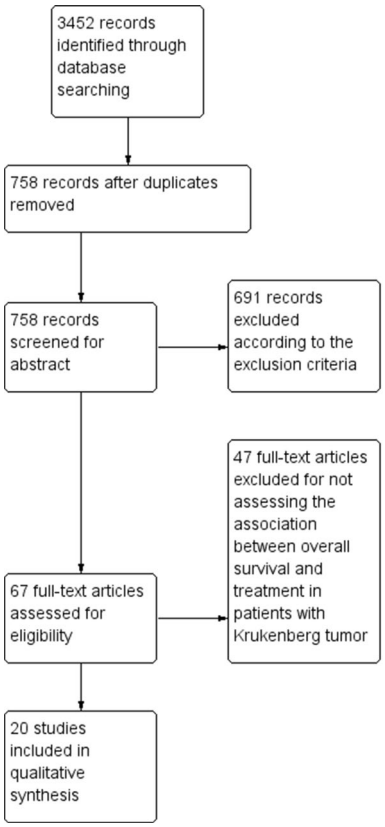

Fig. 1 Flow diagram of studies identified in the systematic review [Prisma template (Preferred Reporting Item for Systematic Reviews and Meta-analyses)]

About the "Bias" domain, nine studies were considered at unclear risk of bias, as they did not carry out multivariate analysis to confirm results [5, 7, 11, 13, 18, 21–24].

About the "Follow-up" domain, one study was considered at high risk of bias due to a follow-up too short in reference to the OS to be assessed [7]; while five studies were considered at unclear risk because they did not specify how long the follow-up was [4, 5, 12, 19, 22].

About the "Loss" domain, three studies were categorized at low risk of bias, while other three studies at high risk of bias because they lost more than 5% of the patients during follow-up [5, 11, 12]. The remaining 14 studies were considered at unclear risk because they did not specify how many patients completed follow-up [4, 7, 10, 13–15, 17–19, 21–25].

Results about risk of bias for each included study were graphically reported in Fig. 2.

Treatments

Seven studies showed that CRS significantly improved OS compared to other treatments or association of treatments without it [4, 6, 13, 15, 17, 19, 22]. This result was also confirmed on multivariate analysis in five studies [4, 6, 15, 17, 19]. Guzel et al. did not show statistical significance about this variable instead [25].

Regarding neoplastic residual, 11 studies showed that CRS without residual (R0 CRS) had a significantly better OS than CRS with residual (R + CRS) [6, 10–14, 18, 20, 21, 23, 24]. Six of these studies confirmed the finding on multi-variate analysis [6, 10, 12, 14, 20, 24]. By contrast, two studies showed no statistical significance about this variable [7, 25].

CT was shown to significantly improve OS at uni- and multi-variate analysis in five studies [4, 10, 14, 17, 19]. However, other five studies did not show statistical significance for this variable [11, 18, 20, 22, 25].

Two articles compared CRS + CT against CT alone [7, 15]. In one study, CRS + CT showed significantly better OS than CT alone [15], while in the other one no significant difference was found [7].

The CRS + CT association was also compared with CRS alone in two studies [14, 23]. In one study, the CRS + CT protocol showed better results at both uni- and multi-variate analysis [14]. Instead, the other one found no statistically significant differences [23].

Regarding HIPEC, Rosa et al. showed that CRS + HIPEC + CT had a higher OS compared to CRS + CT, and compared to CT alone, on both uni- and multi-variate analysis [14]. Furthermore, Wu et al. showed that the CRS + HIPEC had better results than CRS alone, on both uni- and multi-variate analysis [16]. Finally, Cheong et al. found that there was no significant difference in OS between patients treated with CRS + HIPEC and patients treated with CRS + CT [22].

Only two studies assessed neoadjuvant CT in relation to treatment protocols without it [5, 13]. Among these, Ganesh et al. showed a significant lengthening of the OS at univariate analysis, while Seow-En et al. showed no significant differences.

Finally, Seow-en et al. found at univariate analysis that the execution of the CRS in emergency regimen was related to a minor OS compared to its execution in elective regimen.

Results about comparisons amongst OS related to the treatment protocols are summarized in Table 2.

Discussion

Main finding and interpretation

Our study pointed out that several different therapeutic protocols are followed in the treatment of KT. The currently available options for treating this neoplasm are CRS, adjuvant CT, neoadjuvant CT and HIPEC; these treatments may be used alone or in combination.

Table 1 Characteristics of the included studies, patients and KTs

Study (Refs.)	Country	Design	Study period	Mean age years (Range)	Sample size	Primary tumor site				
						Stomach	Colorectal	Mammary	Others	Unknown
Seow-en et al. [5]	Singapore	Retrospective	Jan 2004–Dec 2015	54.2 (± 11.7)	38	4	22	2	9	1
Yu et al. [6]	China	Retrospective	Jan 2005–Dec 2014	43.4	152	152	–	–	–	–
Xu et al. [10]	China	Retrospective	1994–2013	49.3 (± 13.3)	57	–	57	–	–	–
Kammar et al. [7]	India	Retrospective	Jan 2012–Dec 2015	42	25	–	25	–	–	–
Ganesh et al. [13]	USA	Retrospective	Jan 1999–Jan 2015	50	195	–	195	–	–	–
Wu et al. [4]	China	Retrospective	Jan 1990–Dec 2010	48	128	41	58	8	13	8
Rosa et al. [14]	Italia	Retrospective	Jan 1990–Dec 2012	48	63	63	–	–	–	–
Cho et al. [15]	Korea	Retrospective	Mar 2004–Feb 2012	43.4	216	216	–	–	–	–
Wu et al. [16]	China	Retrospective	Jan 2000–Dec 2010	44	62	62	–	–	–	–
Lu et al. [17]	Taiwan	Retrospective	Mar 2000–Jul 2010	44.4	85	85	–	–	–	–
Guzel et al. [25]	Turkey	Retrospective	Jan 2001–Jan 2009	50.1	48	10	20	5	6	7
Jun et al. [18]	Korea	Retrospective	1981–2008	48.6	22	22	–	–	–	–
Kim et al. [19]	Korea	Retrospective	1994–2006	42	34	25	2	–	1	6
Jiang et al. [20]	China	Retrospective	Mar 1997–Dec 2003	44	54	26	23	3	2	–
McCormick et al. [11]	USA	Retrospective	1980–2005	51.5	40	–	40	–	–	–
Ayhan et al. [21]	Turkey	Retrospective	1982–2004	45.2 (± 13.5)	154	35	33	35	33	18
Cheong et al. [22]	S. Korea	Retrospective	1987–1998	45.8	54	54	–	–	–	–
Cheong et al. [12]	S. Korea	Retrospective	1987–2000	44	34	34	–	–	–	–
Kim et al. [24]	Korea	Retrospective	1987–1996	41	34	34	–	–	–	–
Rayson et al. [23]	Canada	Observational	1984–1998	55.8	39	–	39	–	–	–

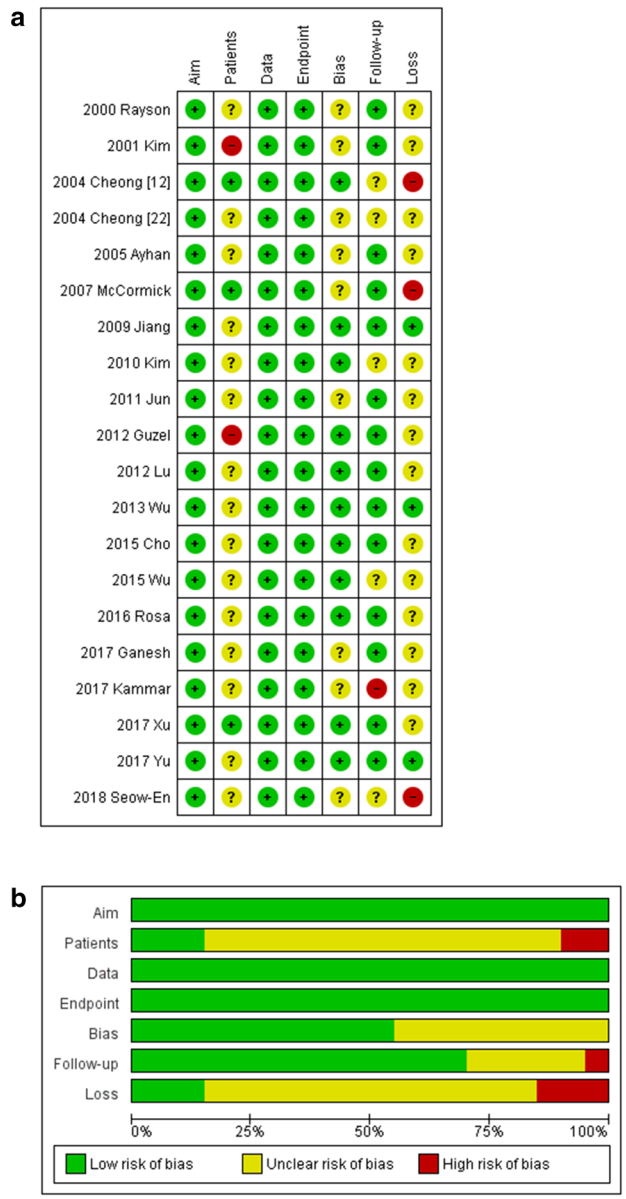

Fig. 2 **a** Assessment of risk of bias. Summary of risk of bias for each study; plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. **b** Risk of bias graph about each risk of bias item presented as percentages across all included studies

To date, it is still not clear which treatment protocol is the most effective one, and the management of patients with KT is not standardized.

Cytoreductive surgery

Many studies reported the effectiveness of CRS in lengthening the OS compared to the absence of such surgical treatment [4, 6, 13, 15, 17, 19, 22]. Furthermore, there is evidence that a radical CRS, in the absence of residuals (R0 CRS), is related to a significant improvement in OS [6, 10–14, 18, 20–24].

In our study, only two articles showed results contrary to these just shown. The first one did not show statistically significant OS improvement either for CRS or for R0 CRS, suggesting that the execution of surgery in all its degree of radicalness is not advisable [25]. The second one analyzed the prognostic value of R0 margins, showing no significant OS improvement compared to R + CRS [7]. This discrepancy in the results might be partly due to some biases in these studies, as already shown in the risk of bias within studies assessment. In particular, study by Guzel et al. seemed to be affected by a selection bias, not differentiating KTs from all other metastatic ovarian tumors in the study sample, while results by Kammar et al. seemed to be affected by a follow-up duration too short to evaluate the efficacy of the treatment. Based on this evidence, it appears deducible that R0 CRS may be essential in the treatment of KT.

Adjuvant chemotherapy

Regarding CT, results about its impact on OS are conflicting. While some studies showed that CT significantly increased OS [4, 10, 14, 17, 19], other ones showed opposite results, with no significant OS improvement [11, 18, 20, 22, 25].

The efficacy of CT was also evaluated in association with CRS in some studies. Two of these studies compared such protocol to CT alone [7, 15], and two others to CRS alone [14, 23]. However, even in this regard, the results are mixed. Compared to CT alone, Cho et al. showed significantly longer OS with the CRS + CT protocol, while Kammar et al. showed no significant difference. Similarly, compared to CRS alone, Rosa et al. showed a significant increase in OS for the combined protocol, while Rayson et al. did not show significant difference. Given these findings, it seems to be not possible to draw any univocal conclusions about effectiveness of CT alone or combined with CRS. Thus, it might be considerable to spare systemic CT for patients with KT, in particular taking account the severe adverse effects and performance status worsening associated with its administration.

Hyperthermic intraperitoneal chemotherapy

Taking into account the above-mentioned considerations on CT, adjuvant therapy with HIPEC might be a good compromise. In the literature, only few studies have been analyzed HIPEC for KTs patients [14, 16, 22]. Rosa et al. assessed the association of HIPEC with CRS and CT. They showed that such association significantly increased OS more than both CRS + CT protocol and CT alone protocol, supporting the independent prognostic value of HIPEC. On the other hand, Wu et al. evaluated the effectiveness

Table 2 Comparisons amongst OS related to the treatment protocols

Study	CRS VS no-CRS				R0 CRS VS R + CRS				CT VS no-CT			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Seow-en et al. [5]	–	–	–	–	–	–	–	–	–	–	–	–
Yu et al. [6]	0.467 (0.318–0.685)	< 0.001	0.486 (0.323–0.729)	< 0.001	–	< 0.001	–	–	–	–	–	–
Xu et al. [10]	–	–	–	–	–	< 0.001	0.135	0.001	–	0.006	0.345	0.012
Kammar et al. [7]	–	–	–	–	–	NS	–	–	–	–	–	–
Ganesh et al. [13]	–	0.003	–	–	–	NR	–	NR	–	–	–	–
Wu et al. [4]	9.346 (4.950–17.544)	< 0.001	4.878 (1.572–15.15)	0.0060	–	–	–	–	0.293 (0.195–0.440)	< 0.001	0.626 (0.371–1.057)	NS
Rosa et al. [14]	–	–	–	–	–	< 0.0001	–	< 0.0001	–	0.0005	–	NS
Cho et al. [15]	0.404 (0.302–0.539)	< 0.001	0.458 (0.287–0.732)	0.001	–	–	–	–	–	–	–	–
Wu et al. [16]	–	–	–	–	–	–	–	–	–	–	–	–
Lu et al. [17]	0.43 (0.26–0.73)	0.002	0.36 (0.19–0.68)	0.002	–	–	–	–	0.14 (0.07–0.27)	< 0.001	0.21 (0.08–0.57)	0.002
Guzel et al. [25]	–	NS	–	–	–	NS	–	NS	–	NS	–	–
Jun et al. [18]	–	–	–	–	–	0.0003	–	–	–	NS	–	–
Kim et al. [19]	1.258*(1.042–1.520)	0.017	1.311*(1.084–1.587)	0.005	–	–	–	–	2469* (1.425–4.273)	0.001	2.347*(1.309–4.219)	0.004
Jiang et al. [20]	–	–	–	–	–	< 0.01	–	< 0.01	–	NS	–	–
McCormick et al. [11]	–	–	–	–	–	< 0.0001	–	–	–	NS	–	–
Ayhan et al. [21]	–	–	–	–	–	0.0039	–	–	–	–	–	–
Cheong et al. [22]	–	0.001	–	–	–	–	–	–	–	NS	–	–
Cheong et al. [12]	–	–	–	–	–	0.0001	–	< 0.0001	–	–	–	–
Kim et al. [24]	–	–	–	–	0.40* (1.17–0.94)	0.036	–	–	–	–	–	–
Rayson et al. [23]	–	–	–	–	–	0.014	–	–	–	–	–	–

Table 2 (continued)

Study	CRS + CT VS CT	CRS + CT VS CRS	CRS + HIPEC + CT VS CRS + CT VS CT	CRS + HIPEC VS CRS				CRS + HIPEC VS CRS + CT	Neoadjuvant CT VS no Neo-adjuvant CT	Emergency VS elective regimen
	Univariate	Univariate	Univariate	Univariate		Multivariate		Univariate	Univariate	Univariate
	P value	*P* value	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	*P* value	*P* value	*P* value
Seow-en et al. [5]	–	–	–	–	–	–	–	–	NS	0.027
Yu et al. [6]	–	–	–	–	–	–	–	–	–	–
Xu et al. [10]	–	–	–	–	–	–	–	–	–	–
Kammar et al. [7]	NS	–	–	–	–	–	–	–	–	–
Ganesh et al. [13]	–	–	–	–	–	–	–	–	0.02	–
Wu et al. [4]	–	–	–	–	–	–	–	–	–	–
Rosa et al. [14]	–	0.0005	0.0005	–	–	–	–	–	–	–
Cho et al. [15]	0.002	–	–	–	–	–	–	–	–	–
Wu et al. [16]	–	–	–	–	0.018	2996 (1.245–7.208)	0.014	–	–	–
Lu et al. [17]	–	–	–	–	–	–	–	–	–	–
Guzel et al. [25]	–	–	–	–	–	–	–	–	–	–
Jun et al. [18]	–	–	–	–	–	–	–	–	–	–
Kim et al. [19]	–	–	–	–	–	–	–	–	–	–
Jiang et al. [20]	–	–	–	–	–	–	–	–	–	–
McCormick et al. [11]	–	–	–	–	–	–	–	–	–	–
Ayhan et al. [21]	–	–	–	–	–	–	–	–	–	–
Cheong et al. [22]	–	–	–	–	–	–	–	NS**	–	–
Cheong et al. [12]	–	–	–	–	–	–	–	–	–	–
Kim et al. [24]	–	–	–	–	–	–	–	–	–	–
Rayson et al. [23]	–	NS**	–	–	–	–	–	–	–	–

HR hazard ratio, *CRS* cytoreductive surgery, *R0 CRS* CRS without residual, *R + CRS* CRS with residual, *CT* adjuvant chemotherapy, *HIPEC* hyperthermic intraperitoneal chemotherapy, *NS* non-significant, * relative risk (no hazard ratio)

of HIPEC in combination with CRS, showing that this association increased the OS about three times on average compared to CRS alone. Finally, Cheong et al. investigated the difference about OS between the CRS + HIPEC protocol and CRS + CT protocol. They did not show any significant difference between the two protocols, concluding that CT and HIPEC might have the same effectiveness if associated with CRS. Despite the low number of studies, HIPEC seems to be effective both alone and in combination with CRS. Furthermore, HIPEC has shown an effectiveness at least equal to CT. Therefore, also given the less severe adverse effects compared to CT, HIPEC seems to be a preferable adjuvant approach for KT.

Neoadjuvant chemotherapy

Little data have been collected on neoadjuvant CT, which seems to be rarely used in KT therapeutic protocols. In the literature, only two studies assessed it, showing conflicting results. In particular, Ganesh et al. showed increased OS with preoperative chemotherapy, while Seow-En et al. did not show statistically significant difference. Therefore, there is no sufficient evidence to advocate or discourage the use of neoadjuvant CT. However, it appears reasonable that neoadjuvant CT might be indicated when R0 CRS is not feasible due to the local extension of KT.

Strengths and limitations

To our knowledge, this may be the first systematic review about treatments of KT. The study aim was to assess which treatment or combination of treatments may be the most effective in terms of increased OS. In fact, to date, treatment of KT is not standardized. Despite the rarity of the disease, this appears as a serious wealth problem, considering the poor prognosis of such patients, due to tumor aggressiveness, advanced stage, diagnostic difficulties and poor treatment efficacy. The low quality of evidence about treatment protocols to be followed, partly due to the tumor rarity itself, also contributes to the poor prognosis. Thus, we tried to improve the quality of evidence, providing a systematic analysis on a relatively large sample ($N = 1533$).

A limit of our study might be the retrospective design of the included studies. Nevertheless, this appears as the only possible study design due to the rarity of KT. In fact, prospective trials would be difficult to perform. Another limit may be the lack of a multi-variate analysis in some included studies. Moreover, the lack of a sufficient number of studies that compared the same treatment or combination of treated precluded the feasibility of a meta-analysis.

Conclusion

CRS and in particular R0 CRS are the treatments that show the clearest results in improving OS in KT patients. Regarding adjuvant CT, results about its effectiveness are conflicting, but it seems that CT cannot replace surgery in a satisfactory way. By contrast, despite being assessed in few studies, HIPEC seems to be not only effective both alone and in combination with CRS, but also related to fewer adverse effect than CT. The usefulness of neoadjuvant CT is still unclear, and seems to be advisable only to try a R0 CRS.

Finally, the association of R0 CRS with HIPEC seems to be the most effective and safe therapeutic protocol for KT patients.

Author contributions RL: study conception, electronic search, eligibility of the studies, inclusion criteria, risk of bias, data extraction and data analysis. MDL: electronic search, eligibility of the studies, inclusion criteria, risk of bias, data extraction and data analysis, and manuscript preparation. AT, AR: study conception, disagreement resolution, and manuscript preparation. GS: electronic search, eligibility of the studies, inclusion criteria, risk of bias, data extraction and data analysis. MM: methods supervision and manuscript preparation. LI: study design, methods supervision, and manuscript preparation. MDA: study design, manuscript preparation, and whole study supervision. FZ: study design, methods supervision, and whole study supervision. FC: study conception and whole study supervision.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

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