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Textbook outcome in ovarian cancer and its impact on survival: comparative study

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Abstract

Introduction Patients who achieve the textbook outcome (TO) present an uneventful postoperative course. Obtaining TO has also been related to better survival in oncological patients. Information about TO in patients with peritoneal carcinomatosis from ovarian cancer who undergo surgery is very scarce. Our objective was investigate TO in patients with carcinomatosis of ovarian origin who underwent interval surgery with or without HIPEC (TOOC) and its impact on survival.

Methods A multicenter study was performed between 2010 and 2015. Inclusion criteria were > 18 years old, with ovarian cancer and peritoneal carcinomatosis, who underwent scheduled surgery after response to neoadjuvant therapy. The criteria to establish TOOC were no major complications, no mortality, non-prolonged stay (p75:10 days), complete cytoreduction (CC-0), and no readmission.

Results 365 patients were included, and TOOC was achieved in 204 (55.9%) patients. CC-0 cytoreduction was obtained in 312(85.5%). 7 patients (1.9%) died. 71 (19.5%) presented major complications (≥ IIIa). The readmission rate was 9.3%, and 24.9% of the patients presented a prolonged stay. The parameter with most significant negative impact on achieving TOOC was length of stay. Multivariate analysis confirmed postsurgical PCI, age, HIPEC, and time of surgery in minutes as an independent factor of TOOC. Survival analysis showed that patients who achieved TOOC had better overall survival (41 months (24.5– 67) versus 27 months (14-48.2) ($p < 0.0001$).

Conclusion TO is an easy and valuable management tool for evaluating and comparing results obtained at different centers after surgery for peritoneal carcinomatosis of locally advanced ovarian cancer. Achieving TOOC benefits overall survival.

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Highlights

- TO is a multidimensional measure that gathers relevant postoperative parameters, permitting the comparison of results between different centers.
- Textbook outcome is and independent factor for survival in every PCI.
- Archieve Textbook outcome in ovarian carcinomatosis has a positive impact on survival.

Keywords Textbook outcome, Benchmarking, Ovarian cancer, Carcinomatosis, HIPEC

Introduction

The quality of cancer surgery is assessed by measuring numerous parameters related to the patient's or tumor's characteristics, postoperative morbidity, and disease-free survival [1]. In surgery, benchmarking strategies have evolved considerably over recent decades, and the appearance of pathology-specific benchmarks is also becoming increasingly more common [2].

In 2013, the first definition of textbook outcome (TO) appeared, gathering several benchmarks to reflect the ideal result of a surgical procedure with an uneventful peri- and postoperative course and excellent oncological results [3]. Length of hospital stay, mortality, readmission, peri-operative complications, stoma preparation, readmission to the ICU, and complete resection (R0) were used to define TO in colorectal cancer surgery. Since then, interest in applying this new quality tool has exponentially increased, with emerging definitions of TO in almost all surgical areas, such as hepatopancreatobiliary, esophagogastric, and bariatric surgery [4–6].

Ovarian cancer of epithelial origin is the sixth most common cancer in women and the primary cancer-related death in this population. Due to its slow growth, most patients remain asymptomatic, and 80% debut with ascites and peritoneal carcinomatosis. The standard treatment for the initial management of advanced tubo-ovarian carcinoma is primary cytoreductive surgery (PCS) or, in those not considered suitable for upfront surgery, NACT followed by intervalic surgery. Bevacizumab and as first- and second-line treatment for advanced epithelial ovarian, fallopian tube, and primary peritoneal cancers. Its use in OC is primarily based on the positive results of some randomized clinical trials showing improved survival rates with the addition of bevacizumab to standard first line chemotherapeutic drugs, mainly in high-risk patients and to second-line treatment both in platinum sensitive and platinum-resistant disease [7–9]. For patients with FIGO stage IIIc, when a complete cytoreduction cannot be achieved, neoadjuvant therapy followed by CC-0 cytoreductive surgery (CRS), with or without hyperthermic intraperitoneal chemotherapy

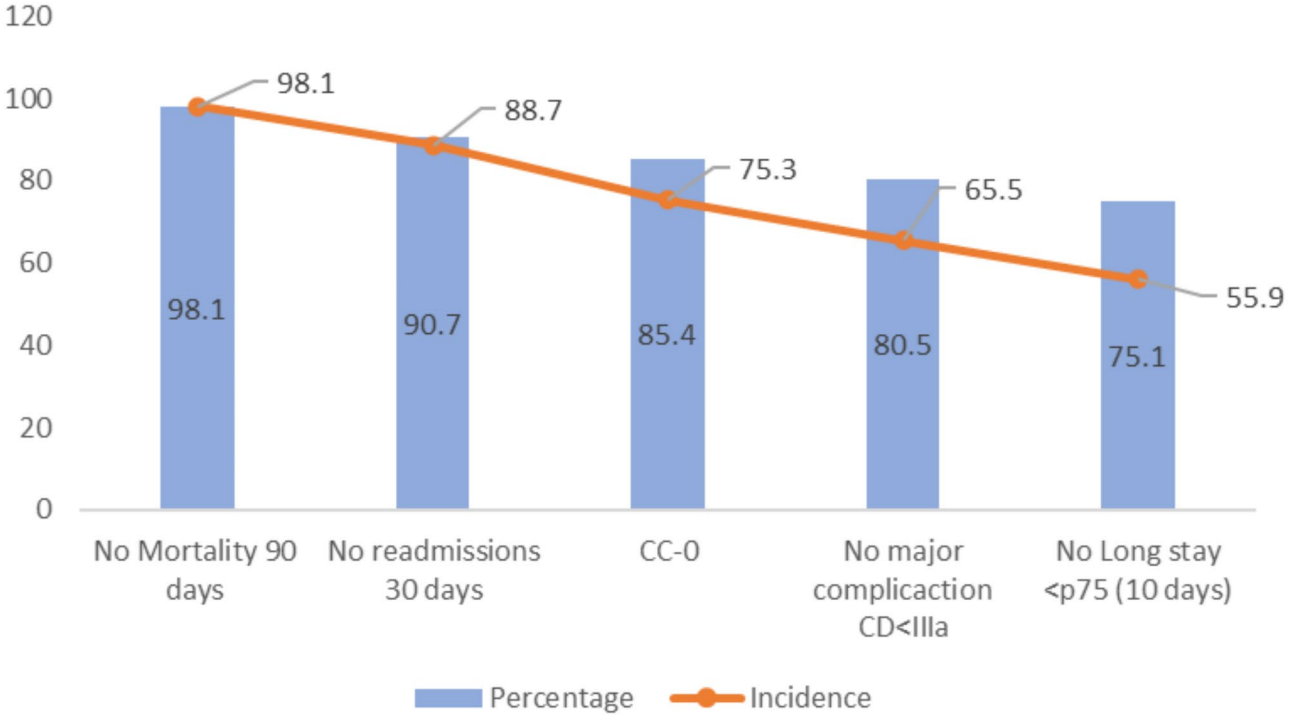

Fig. 1 Textbook outcome in ovarian carcinomatosis. (TOOC)

(HIPEC), has proven to be the best treatment providing the best long-term survival rates [8, 9]. Nevertheless, an appropriate cytoreductive surgery may require a high level of specialization, being associated with high morbidity rates, around 20 to 60%, and mortality rates between 5 and 10% [4, 10]. Definition of benchmarks in the field of peritoneal carcinomatosis remains troublesome because a wide range of therapeutic scenarios is possible depending on the type of tumor or which protocol of HIPEC was used. This fact means that the results of the published studies vary widely, and it is not easy to establish clear follow-up guidelines [11, 12]. Only two studies have assessed the TO in ovarian peritoneal carcinomatosis by applying (using) different criteria or analyzing various types of tumors [13, 14].

The present study aims to assess the TO in a series of patients with peritoneal carcinomatosis of ovarian origin undergoing interval CRS with or without HIPEC and to evaluate the impact of TO on overall survival.

Materials and methods

Study design and setting

A multicenter retrospective observational study was performed between 2010 and 2023 from a prospective database on all patients with peritoneal carcinomatosis of ovarian origin undergoing or that underwent interval CRS (with or without HIPEC) and subsequent adjuvant treatment from 3 referral centers for the treatment of peritoneal carcinomatosis.

Each center's multidisciplinary clinical committee decided whether to administer neoadjuvant therapy or not to specific patients. The inclusion criteria were patients over 18 years of age, with peritoneal carcinomatosis from ovarian origin, who underwent scheduled surgery with curative intent after response to neoadjuvant therapy. The study followed the guidelines for Strenghtening the Reporting of Observational Studies in Epidemiology (STROBE) [15]. The study is registered in www.researchregistry.com/with the unique identification number (UIN) 10,306. The medical ethics committee judged that no informed consent from the patients was necessary because of the observational nature of the study without additional burden for the patient. Ethical approval for this study (Ref. CEIm: PI2023-070) was provided by the ethical Committee of Alicante, ISABIAL institute on 11 September 2023. Ethical committee waived informed consent due to retrospective nature and entailed no risk for patients. Planning and analysis of the study was carries out according to the STROCCS Reporting Guidelines for Cohort Studies [16]. Data are in a repository and could be requested to main author under are justified application.

Patients

Patient characteristics, tumor, and treatment data were obtained from a database created using written and electronic medical records to carry out the study. Comorbidity was evaluated according to the ASA score and the Charlson index [17, 18]. The tumor stage was classified according to FIGO classification [19]. The postoperative complications were collected according to the Clavien-Dindo classification [20]. Postoperative complications ≥ IIIa were considered major complications.

Textbook outcome

Based on the definitions of TO applied in other surgical areas and in agreement with Algera et al., [14] the criteria used to establish TO from ovarian origin (TOOC) were the following: (i) no Clavien-Dindo complications ≥ IIIa, (ii) absence of mortality at 90 postoperative days, (iii) non-prolonged length of stay (LOS) which was established according to the p75 of the series, (iv) achieving complete cytoreduction (CC-0), and (v) no re-admission within 30 days. Overall survival (OS) was calculated from surgery to death due to any cause or the date of the last follow-up.

Statistical analysis

Quantitative variables, median, and interquartile range (IQR) were determined; variables were compared using the Chi-squared and continuous variables with the non-parametric Mann-Whitney U test. Patient characteristics, tumor, histology, and treatment were compared between patients who achieved TOOC and patients who did not. The Kaplan-Meier curves and log-rank test were used to compare the survival of patients with or without TOOC. Logistic regression analysis evaluated the association of different factors affecting TOOC achievement. P value < 0.05 was considered statistically significant. The study was performed with SPSS v.25®.

Results

Textbook achieved parameters

A total of 365 patients were included. Complete CC-0 cytoreduction was achieved in 312 (85.5%). Seven patients (1.9%) died within 90 days after CRS. Seventy-one patients (19.5%) presented major complications. The 30-day readmission rate was 9.3%. The prolonged median length of hospital stay (LOS) was ten days, and 75.1% of the patients did not surpass it. Calculating the cumulative incidence of all the parameters that comprise TOOC, 204 patients (55.9%) achieved it. The parameter with the most significant negative impact on achieving TOOC was the length of stay, followed by major complications, incomplete cytoreduction, and readmissions. Mortality was the less frequent parameter that predicted the achievement of TOOC (Fig. 1).

Table 1 Characteristics of patients who achieve TO versus non-TO

	Non TO *n*(%) 161 (44.1)	**TO *n*(%) 204 (55.9)**	***p* value**
PATIENTS CHARACTERISTICS			
Age*	64 (56.8–67.1)	58.1 (55.1–68.0)	< 0.0001
BMI median (IQR)	25.9 (22.6–29)	25.9 (22.8–29.6)	0.45
ASA			0.12
1	8 (5.0)	7 (3.4)	
2	63 (39.1)	105 (51.5)	
3	85 (52.8)	88 (43.1)	
4	5 (3.1)	4 (2.0)	
Charlson age score*	2(2–3)	2(1–3)	< 0.001
Histology			0.23
• Low grade	1 (0.3)	0 (0.0)	
• High grade	147 (40.3)	188 (51.5)	
• Endometroid	3 (0.8)	7 (1.9)	
• Others	2 (0.5)	8 (2.2)	
Preoperative DATA			
Hb * g/dL	12 (1.8–12)	12 (11–12)	0.68
Neutrophils*) l/mm^3	5305 (3810–7230)	5390 (3990–6810)	0.96
Lymphocytes * l/mm^3	1410 (1220–1890)	1410 (1190–1480)	0.46
Platelets *x10^3/µL	232.000 (194.000–29.000)	22.000 (165.000-287.000)	0.34
CEA * ng/mL	1.93 (1.40–2.40)	2 (1.3–2.6)	0.88
CA 125 * ng/mL	53 (23–236)	31 (16–163)	0.04
CA19.9 *ng/mL	22.65 (13.6-48.45)	11 (7–35)	0.06
HE4 *U/mL	136 (94–193)	71 (63–100)	0.02
INTRAOPERATIVE DATA			
Surgical time (min)	350 (300–450)	300 (250–375)	< 0.0001
Total PCI			< 0.0001
< 10	51 (14)	143 (39.3)	
11–20	59 (16.2)	51 (14.0)	
> 20	50 (13.7)	10 (2.7)	
PCI median (IQR)	15 (8–22)	6 (3–12)	< 0.0001
Intestinal resection			< 0.0001
No	79 (21.6)	153 (41.9)	
Yes	82 (22.5)	51 (14)	
Anastomosis number			< 0.0001
1	80 (21.9)	155 (42.5)	
2	60 (16.4)	43 (11.8)	
3	19 (5.2)	6 (1.6)	
4	2 (0.5)	0 (0)	
HIPEC			0.04
No	35 (9.6)	28 (7.7)	
Yes	126 (34.5)	176 (48.4)	
HIPEC			0.14
Cisplatin	42 (11.5)	73 (20)	
Paclitaxel	84 (23)	102 (27.9)	
Time to return chemotherapy*	6 (5–8)	4 (4–6)	< 0.0001
POSTOPERATIVE RESULTS			
Clavien Dindo Complications **			< 0.0001
0	30 (8.2)	122 (33.4)	
I	2 (0.5)	10 (2.7)	
II	58 (15.9)	72 (19.7)	
IIIa	37 (1.1)	0 (0.0)	
IIIb	15 (4.1)	0 (0.0)	
Iva	4 (1.1)	0 (0.0)	
IVb	8 (2.2)	0 (0.0)	
V	7 (1.9)	0 (0.0)	

Table 1 (continued)

	Non TO *n*(%) 161 (44.1)	TO *n*(%) 204 (55.9)	*p* value
C reactive protein (CRP) 3º day*	124 (101.3-116.9)	63.5 (31.9–86.5)	0.003
C reactive protein (CRP) 5º day*	117.1 (84.1-196.2)	36.4 (10–45)	0.001
Medical complication			< 0.001
No	104 (28.5)	187 (51.2)	
yes	57 (15.6)	17 (4.7)	
Surgical complication			< 0.001
No	95 (26)	189 (51.8)	
Yes	66 (18.1)	15 (4.1)	
Fistula or dehiscence			0.01
No	156 (42.7)	204 (56.4)	
Yes	5 (1.4)	0 (0.0)	
SSI superficial			0.14
No	156 (42.7)	202 (55.3)	
YES	5 (1.4)	2 (0.5)	
Ileus			0.14
No	145 (39.7)	197 (54)	
Yes	16 (4.4)	7 (1.9)	
Catheter infection			0.05
No	158 (43.6)	204 (55.9)	
Yes	3 (0.8)	0 (0.0)	
Relapse			0.32
No	52 (14.2)	76 (2.8)	
Yes	109 (29.9)	128 (35.1)	
Length of stay (days) **	11 (7–14)	7 (5–8)	< 0.001
Survival in months after surgery median (IQR)	27 (14-48.2)	41 (24.5–67)	< 0.0001

*median and IQR; ** this parameters are into TOOC definition; Hb: Hemoglobin; BMI: Body mass index; SSI: surgical siteinfection

Comparison of TOOC and non-TOOC groups

Comparison of the TOOC and non-TOOC groups revealed less median age (58 vs. 64, shorter surgical time in minutes 300 vs. 350, lower preoperative levels of CA125 (31 vs. 53), and lower levels of He4 (71 vs. 136), C-reactive protein (CRP) levels at 3postoperative day (63.5 vs. 124), age-adjusted scores on the Charlson scale, and peritoneal cancer index (PCI) (6 vs. 15). However, there were no significant differences in BMI, presurgical hemoglobin, leukocytes, lymphocytes, platelets, or CEA levels. There were also no differences in tumor histology (defined as high-grade in 91.8% of patients), the type of drug used for the HIPEC procedure, or surgical wound infection. (Table 1)

Regarding surgical factors, the patients who achieved the TOOC had fewer intestinal resections (41.9% versus 21.9%) and fewer anastomoses (42.5%, only one). HIPEC was administered more often to patients in the TOOC group (48.2%) than to patients who did not have it (34.5%). As was expected, the TOOC group presented fewer overall medical complications and lower rates of surgical complications (both major and minor), including less anastomotic leakage (0.0% vs. 1.4%) and postsurgical ileus (1.9% vs. 4.4%). Central venous catheter infection was more frequent in the non-TOOC group. Adjuvant chemotherapy was initiated earlier in the TOOC group (six versus four weeks) $p < 0.0001$).

Univariant and multivariant analysis

The univariate analysis showed age, shorter surgical time, and the addition of HIPEC as independent factors associated with the achievement of TOOC, as well as lower PCI and fewer intestinal resections and anastomoses. Restart chemotherapy after surgery was earlier in the TOOC group. Other independent factors for achieving TOOC were the presence of postsurgical paralytic ileus and overall medical and surgical complications. The multivariate analysis confirmed lower age, lower PCI, administration of HIPEC, and shorter surgical time as predictors of the achievement of TOOC. Table 2 shows the results of the univariate and multivariate analyses.

Survival analysis

The survival analysis showed a better median overall survival in patients who achieved TOOC (median 41 versus 27 months) (log-rank $p < 0.0001$). Figure 2 shows the survival of the two groups. Finally, a survival analysis stratifying by PCI (< 10;10–20;>20) and TOOC was carried out; the patients who reached the TOOC patients showed significantly longer overall survival in all PCI categories. These data are provided in Supplementary File 1.

Table 2 Univariant and multivariant analysis of independent factors for achieve TOOC

	Univariant analysis				Multivariant analysis			
	OR	**IC95% inf**	**IC 95% sup**	***p* value**	**OR**	**IC95% inf**	**IC 95% sup**	***p* value**
Age	*0.96*	*0.94*	*0.98*	*0.00*	0.97	*0.99*	*0.99*	*0.02*
Time surgery in min	*0.9*	*0.99*	*0.99*	*0.00*	*0.99*	*0.99*	*0.99*	*0.00*
HIPEC No (ref.) Yes	*1.75*	*1.01*	*3.02*	*0.04*	*3,22*	*1.54*	*6.75*	*0.00*
Number of anastomosis 1 ref 2 3 4	*0.38*	*0.27*	*0.54*	*0.00*	*0.43*	*0.15*	*1.23*	*0.12*
preoperative CA 125	*1*	*0.99*	*1.00*	*0.50*	-	-	-	-
preoperative HE4 preoperative	*0.97*	*0.94*	*1.00*	*0.74*	-	-	-	-
C Reactive protein 3º day	*0.97*	*0.96*	*0.96*	*0.00*	-	-	-	-
C Reactive protein 5º day	*0.96*	*0.93*	*0.99*	*0.020*	-	-	-	-
Charlson score	*0.97*	*0.90*	*1.05*	*0.54*	-	-	-	-
PCI < 10 11–20 > 20 ref.	*14.02* *4.32*	*6.61* *1.99*	*29.69* *9.38*	*0.00* *0.00*	*12.45* *3.97*	*5.40* *1.73*	*28.64* *9.11*	*0.00* *0.00*
Intestinal resection No (ref.) Yes	*3.1*	*2.0*	*4.84*	*0.00*	*1.78*	*0.88*	*3.61*	*0.10*
Fistula or dehiscence No Yes	*0.00*	*0.00*	-	*0.99*	-	-	-	-
Ileus No ref. Yes	*3.10*	*1.24*	*7.74*	*0.02*	*4.9*	*0.12*	*1.4*	*0.15*
Catheter infection No ref. Yes	*21*	*0.00*	-	*0.99*	-	-	-	-

Discussion

TO is a multidimensional measure that gathers relevant postoperative parameters, permitting the comparison of results between different centers. In this study, we recorded a TOOC of 55.9%, which is very similar to the 54% published in a study from the Netherlands [16]. However, we included readmission as an additional parameter omitted in that study. The decision to do so is debatable since the readmission rate is often related to whether discharges are made early. However, including readmissions in the assessment of TOOC is an important measure of quality control since most readmissions are associated with complications, and initially, including these patients as TOOC when they were not, would have introduced a bias in the TOOC assessment. If we had not included this parameter, our TOOC rate would have been 58.6%.

Another distinctive feature of our study is assessing postoperative mortality at 90 days. Several publications support the mortality measurement to be performed at 90 days because the mortality rate may double if only 30 days or in-hospital mortality is used [19], and this fact may explain why our mortality rate was more than twice that previously reported (0.8% versus 1.9%) [16]. Both mortality rates are considered within the published quality standards for peritoneal carcinomatosis (< 5% 30-day mortality) [12, 13]. The main reason for the lower rate of TOOC achieved in our study was the prolonged stay, which in our research was ten days, coinciding with the cut-off point applied previously [16]; however, those authors did not calculate it using the p75 but considered that stays > 10 days reflected a delay in the start of adjuvant treatment after surgery, an important prognostic factor for survival.

Likewise, as in previous publications [16], we did not include the time until the restart of chemotherapy < 6 weeks in our definition of TOOC. However, the time to restart adjuvant chemotherapy was also significant, suggesting that adjuvant chemotherapy should probably be added for TOOC. Numerous publications that have

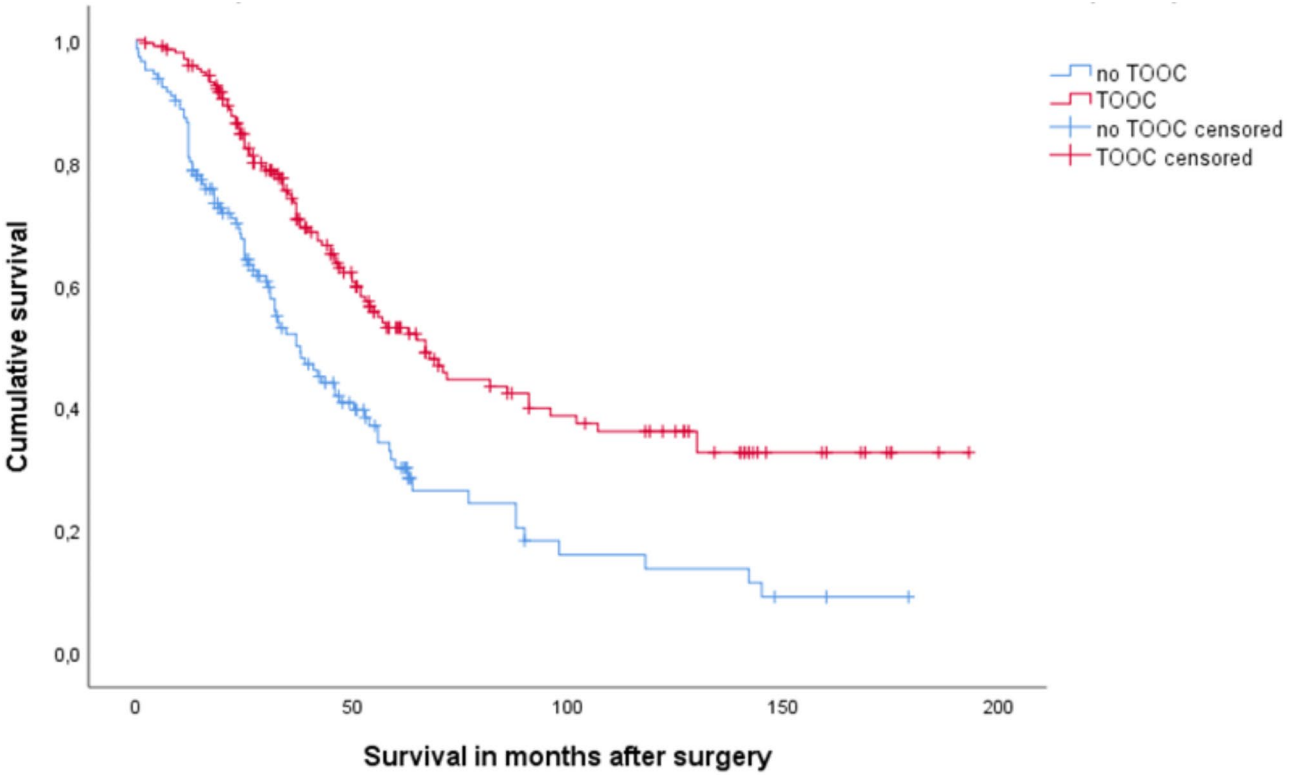

Fig. 2 Kalpan- Maier curve for textbook outcome in Ovarian Carcinomatosis (TOOC)

associated this issue with better disease control, lower recurrence rates, and longer disease-free time and survival strengthen this approach [21, 22].

In our study, lower age, and low PCI (< 10), shorter time to surgery, and addition of HIPEC were predictive of the achievement of TOOC after the multivariate analysis. The Netherlands´ study only found age < 70 years to be a significant factor in failing to obtain the TOOC [16]. In our study, age was an independent factor for TOOC in the multivariate analysis. This data agrees with other studies in which increasing age is associated with a reduction in TO [23, 24] PCI is associated with a higher rate of TOOC achievement greeted achievement of TOOC. This is probably because the higher the PCI leads to an increased greater number of visceral resections and anastomoses, and the higher the postoperative morbidity rates [25–27].

Some clinical trials show that the use of HIPEC during the interval cytoreduction to treat patients with ovarian cancer after neoadjuvant therapy and cytoreduction plays a role in increasing improved survival in these patients in clinical trials and should be considered in the first surgery of patients with ovarian cancer with peritoneal dissemination treated with neoadjuvant systemic chemotherapy [10, 11, 28]. In the multivariate analysis, patients who received HIPEC were significantly more likely to achieve the TOOC than those who did not in the multivariate analysis. Although HIPEC is associated with nephrotoxicity, it does not increase the rest of the complications. This result is consistent with other studies that have demonstrated the safety of HIPEC and its low impact on postoperative morbidity [29–31].

As regards survival, patients who achieved TOOC survived a median of 14 months longer. The two curves remained separated from the beginning, and although the benefit was constant throughout the follow-up period, it was most remarkable for long-term survival (which is where the curves separate the most). These findings agree with other TO series, which have observed a direct and significant relationship between TO and increased survival [32–40]. A fact that reinforces and increases the value of achieving TOOC on survival is that, regardless of the patient's surgical PCI, in all groups, the achievement of TOOC was associated with a statistically significant survival benefit. The two previously published series did not include the relationship between PCI and TO, so we could not compare them with our results.

Our study presented certain limitations. We should mention the retrospective observational nature of the data, with the possible biases that this approach entails. We did not include the time to restart chemotherapy after surgery as a TOOC parameter and the scarce of literature of TO in carcinomatosis. On the other hand, the study has specific strengths, such as novelty, its

multicenter design in referral carcinomatosis centers, prospective databases, and long follow-up periods.

In conclusion, the TOOC is a valuable tool to compare the results obtained in patients with peritoneal carcinomatosis of ovarian origin undergoing interval surgery at different centers. The achievement of TOOC has a positive impact on survival.

Abbreviations

TO	Textbook outcome
ICU	Intensive care unit
CRS	Cytoreductive surgery
HIPEC	Hyperthermic intraperitoneal chemotherapy
ASA score	American society of anesthesiologist
TOOC	Textbook outcome ovarian cancer
LOS	Length of stay
CC-0	Complete cytoreduction
OS	Overall survival
IQR	Interquartile range
CRP	C-reactive protein
PCI	Peritoneal cancer index
BMI	Body mass index
STROBE	For strenghtening the reporting of observational studies in epidemiology

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03686-5.

Supplementary Material 1

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No

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Role Definition Conceptualization CARBONELL, ARJONA, CASCALES, LACUEVA, RAMIA; Data curation SILVIA CARBONELL-MOROTE; ALIDA GONZÁLEZ GIL; GONZALO GÓMEZ DUEÑAS; ELENA GIL GÓMEZ; IBAN CARAVACA; VERONICA ARANAZ; Formal analysis CARBONELLFunding acquisition NO FUNDS; Investigation SILVIA CARBONELL-MOROTE; ALIDA GONZÁLEZ GIL; GONZALO GÓMEZ DUEÑAS; ELENA GIL GÓMEZ; IBAN CARAVACA; VERONICA ARANAZ; Methodology CARBONELL, RAMIA; Project administration CARBONELL, RAMIA; Resources Software CARBONELL; Supervision CARBONELL, RAMIA; Validation CARBONELL, ARJONA, CASCALES, LACUEVA, RAMIA; Visualization CARBONELL, RAMIA; Writing – original draft CARBONELL; Writing – review & editing CARBONELL, ARJONA, CASCALES, LACUEVA, RAMIA.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Study approved Ethics Committee of Hospital General Universitario Dr. Balmis (Ref. CEIm: PI2023-070). The study followed the guidelines for Strenghtening the Reporting of Observational Studies in Epidemiology (STROBE). The study is registered in www.researchregistry.com/with the unique identification number (UIN) 10,306. The medical ethics committee judged that no informed consent from the patients was necessary because of the observational nature of the study without additional burden for the patient. Including the waiver of informed consent and consent for participate due the retrospective nature of the study, entailed no risk. (Page 7).

Consent for publication

Not applicable. Waived for ethics Committee (Page 7).
Provenance and peer review not commissioned, externally peer-reviewed.

Competing interests

The authors declare no competing interests.

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