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Effect of perioperative COX-2 and beta-adrenergic inhibition on 5-year disease-free-survival in colorectal cancer: A pilot randomized controlled Colorectal Metastasis PreventIon Trial (COMPIT)

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ABSTRACT

Introduction: Based on translational and epidemiological evidence, perioperative inhibition of beta-adrenergic and COX2 signaling can reduce the risk for post-surgical metastatic disease. Here we aimed to assess in a pilot study the impact of a perioperative combined COX-2 and beta-adrenergic blockade on long-term cancer outcomes in colorectal cancer patients undergoing curative surgery.

Materials and methods: Thirty-four newly diagnosed colorectal cancer patients without evidence of metastases enrolled in this double-blinded placebo-controlled randomized clinical trial (treatment, n = 16; placebo, n = 18). A 20-day oral treatment of propranolol and etodolac regimen was initiated 5 days before surgery. Beneficial effects on short-term molecular biomarkers of cancer progression were reported earlier. Here we present outcomes of five postoperative years of disease-free-survival and overall survival.

Results: Adverse event rates were equivalent between the two groups. Intent-to-treat analyses of 5-year follow-up showed that 2/16 (12.5%) vs 9/18 (50%) patients exhibited recurrence in treatment vs placebo groups, respectively ($p = 0.033$), and 2/16 (12.5%) vs 4/18 (22%) died ($p = 0.467$). In protocol compliant patients 0/11 (0%) vs. 8/17 (47%) exhibited recurrence in treatment vs. placebo groups, respectively ($p = 0.007$), and 0/11 (0%) and 3/17 (17.6%) died ($p = 0.151$).

Conclusions: In this pilot clinical trial, a combined perioperative treatment with propranolol and etodolac significantly improved 5-year disease-free-survival. The small sample size and a single center study design merits caution in interpreting these results, specifically in estimating the effect-size. Larger studies in colorectal cancer are warranted and needed.

1. Introduction

Surgery is the cornerstone of curative treatment of colorectal cancer (CRC). Yet, a significant portion of the patients will eventually experience cancer recurrence, which may lead to their death [1,2]. Preclinical research indicates that several biological processes that occur specifically during the perioperative period can increase the likelihood of disease progression and recurrence, including shedding of tumor cells, suppression of cell mediated immunity, inflammation and adrenergic signaling [3,4]. These effects were shown to be mediated in part through neuroendocrine responses involving perioperative release of prostaglandins and catecholamines, which can inhibit anti-metastatic cell-mediated immunity, induce pro-metastatic molecular processes in tumor cells, and alter tumor micro-environment in a pro-malignant

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manner [3–6]. Moreover, catecholamines adversely impact most hallmarks of cancer [6], and prostaglandins mediate inflammation, which in itself is a hallmark of cancer [7]. Recent reports identified early post-operative inflammation as a predictor of CRC recurrence [8]. Thus, and as also elaborated elsewhere [9–11], transient biological processes that occur during the short perioperative period (days and weeks surrounding cancer surgery) can disproportionately impact long-term disease outcomes following cancer surgery.

To block these detrimental perioperative effects, we have conducted two small phase-II randomized controlled biomarker trials, testing combined blockade of prostaglandins and catecholamines using a regimen of etodolac (a semi-selective COX-2 inhibitor) and slow-release propranolol (a non-selective beta-blocker) in colorectal [12] and in breast [13,14] cancer patients undergoing surgery with curative intent. Following promising biomarker results, indicating anti-metastatic molecular changes in excised tumor samples [12–14], and a statistically non-significant trend toward beneficial DFS outcomes [15], the aim of the current study is to assess 5-year disease-free-survival (DFS) and overall survival (OS) in the CRC cohort (COMPIT- Colorectal Metastasis PreventIon Trial, NCT00888797), with the purpose of assessing long-term safety outcomes and cancer outcomes, needed to justify larger clinical trials powered to assess effect size and advance toward potential clinical implementation.

2. Materials and methods

Patients undergoing colon and rectal surgery for biopsy proven colorectal adenocarcinoma with curative intent were recruited, between May 2010 to March 2015, at a single tertiary medical center. Patients with metastatic disease at presentation, patients with any listed contraindication for the use of etodolac or propranolol, and patients chronically treated with prostaglandins or catecholamine blockers were excluded from this study. For inclusion and exclusion criteria see Supplementary Material 1.

Patients were randomly assigned (in randomization blocks of 10, 1:1 ratio) to receive oral propranolol and etodolac or placebo. Patients were followed with a predefined follow-up protocol for five years to determine cancer recurrence and survival.

The intervention phase included a 20-day treatment regimen. Treatment initiated 5 days before and ended two weeks after surgery. Slow-release propranolol was administered orally at initial dose of 20 mg b.i.d for 5 days; increased to 80 mg b.i.d. on the day of surgery; and decreased to 40 mg b.i.d. for 7 days postoperatively and 20 mg b.i.d. for additional 7 days. Etodolac was administered orally at a constant dose of 400 mg b.i.d. for the entire treatment duration. Placebo pills were identical in weight and color, and were administered according to the same schedule. Study medications were prepared by Superpharm Professional Ltd (Petach Tikva, Israel), which conducted compounding of propranolol, etodolac, and placebo capsules in accordance with ISO 9001:2015 and Good Preparation Practices.

Patients were followed for 5-years to assess recurrence and survival rates. Follow-up continued until completion, until recurrence/death were recorded, or until withdrawal from the study, with the exception of 3 patients that were lost to DFS follow-up. For DFS analysis, complete data was available for 12/16 intervention patients (2 were lost to follow-up and 2 withdraw from the study), and for 16/18 control patients (1 was lost to follow-up and 1 withdraw from the study, see CONSORT diagram). For OS analysis, data was available for all patients (either through medical records or the national registry).The follow-up visits were conducted at 1, 3, 6 and 12 months, and then annually up to 5-years. Each visit included physical examination, CEA levels assessment, imaging including contrast enhanced chest and abdomen CT or PET-CT. Colonoscopy was conducted at one year and four years from surgery. . Patients were allowed to receive any kind of adjuvant therapy as per clinical judgment. Diagnosis of recurrent disease was considered exit points of the study, to allow the patients to receive any kind of oncologic therapy, including investigational ones. Patients' follow-up and the census were used to determine overall survival. DFS was defined, as suggested by Punt et al., 2007 [16], as survival time with no evidence of any malignant disease (local regional, metastatic, new-primary) or death (from any cause) during the 5 post-operative years (see Supplementary Material 2 for detailed definition).

The study was planned to be a pilot clinical outcomes trial, and a biomarkers study. Power analysis was calculated to allow sufficient power for the biomarkers study [12], and was not meant to be adequately powered for DFS and OS. Intent-to-treat (ITT) analyses were first conducted as primary analyses followed by secondary analyses of protocol-compliant patients, which was defined as taking at least 60% of the study medications throughout the intervention phase, and at least 75% in the pre-operative period. We compared treatment effects on DFS and OS by employing Kaplan-Meier survival curves [17], and the log-rank tests to assess survival distributions differences between drug and placebo treatments. Given the small sample size and low event number, addressing additional covariates is not recommended statistically. Differences between groups in demographic and clinical characteristics were assessed using the chi-square test or the Fisher exact test. All graphs are based on actual data.

The study protocol (COMPIT- Colorectal Metastasis PreventIon Trial, NCT00888797) was approved by the local institutional review board and all patients provided informed consent.

3. Results

3.1. Sample characteristics

Thirty-four patients undergoing surgical resection for CRC, at a median age of 58 (30–77) years, were recruited and randomized. CONSORT flowchart is shown in Fig. 1. There were no statistically significant differences in demographic and clinical characteristics of the two groups. Gender distribution in intent-to-treat patients showed marginally significant higher male proportion in the Intervention group (Intervention group: 11 Men, 5 Women, Placebo group: 6 Men, 12 Women, $p = 0.089$). See discussion for potential impact on outcome. Demographic and clinical characteristics are shown in Table 1.

3.2. 5-Year disease-free survival

Disease-free survival at five years was significantly improved in patients who received perioperative propranolol and etodolac compared to the placebo group. In the ITT analysis, recurrent disease was diagnosed in 2/16 patients (12.5%) in the treatment group, versus 9/18 patients (50%) in the placebo group (Fig. 2). In each group, one patient was unexpectedly diagnosed with metastatic disease already at the time of surgery. Mean DFS time was 53.3 months (CI: 44.45–62.04) in the treatment group and 40.65 months (CI: 30.1–51.2) in the control group, which significantly differed by log-rank test ($p = 0.033$).

The difference between the groups became even more prominent in the protocol-compliant analysis. None (0/11) of the patients in the treatment group exhibited recurrence, vs 8/17 patients (47%) in the placebo group (Fig. 3). A log-rank test showed a significant group difference ($p = 0.007$).

3.3. 5-Year overall survival

For both ITT and protocol-compliant analyses, there was a

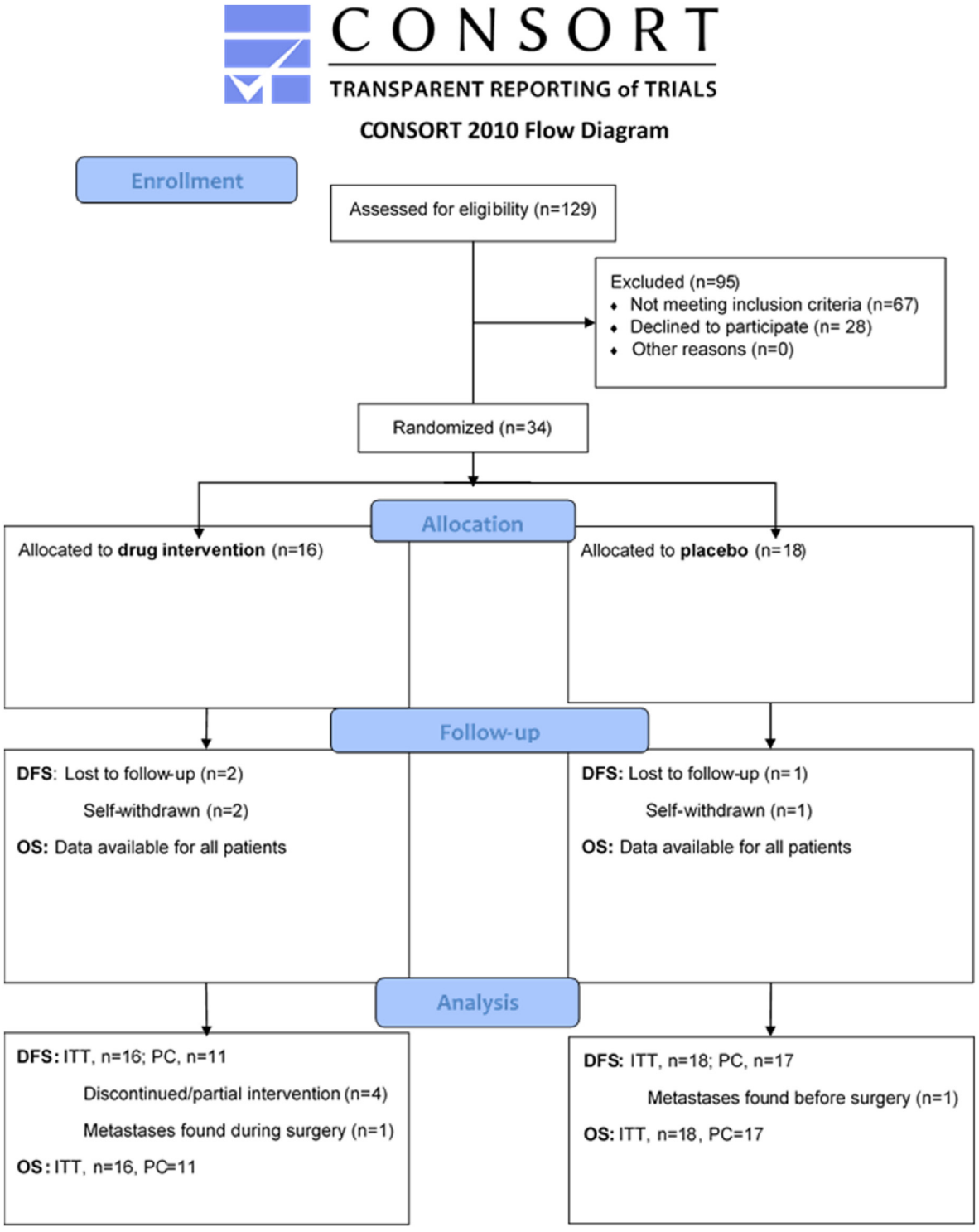

Fig. 1. CONSORT diagram.

pattern of better OS in the treatment group, but this difference did not reach statistical significance. Two out of 16 patients in the ITT analysis died in the treatment group vs. 4/18 patients in the control group ($p = 0.47$). In the protocol-compliant analysis, none of the treatment group patients (0/11) died vs. 3/17 in the placebo group ($p = 0.151$).

Importantly, gender did not significantly predict DFS outcomes for both ITT and protocol compliant (PC) log-rank analyses, $p > 0.097$) and thus it is not likely to be a source of significant confounding for the primary analyses. Also, although not statistically significant, fewer patients in the treatment group (50% Vs.72% in placebo) had T3 tumors, as indicated by the pathology report of the resected specimen. Notably, in each of the T status sub-groups, the beneficial effects of the treatment were separately evident (5-year DFS rates in treatment vs placebo, respectively: for $T = 3$, ITT: 87.5% vs 50%; PC: 100% vs 53.8%; and for $T < 3$, ITT:, 85.7% vs 50%; PC < 3, 100% vs 50%). There was no difference in the rate of nodal disease.

Table 1
Baseline demographic and clinical characteristics.

Table 1: Baseline demographic and clinical characteristics of (i) all 34 randomized patients, (ii) 28 protocol compliant patients

		Intent-To-Treat Analyses (n = 34)		P-Val	protocol-Compliant Analyses (n = 28)		P-Val
		Placebo (n = 18)	Drugs (n = 16)		Placebo (n = 17)	Drugs (n = 11)	
Age at surgery Mean		54.8	57.6	0.501	55.7	57.4	0.718
(MIN, MAX)		(39,73)	(30, 77)		(40,73)	(30, 77)	
BMI Mean		26.6	25.1	0.37	27	25.6	0.445
(MIN, MAX)		(18.7, 36.6)	(15.6, 33.7)		(21.8, 36.6)	(15.6, 33.7)	
Weight Mean		72.8	71	0.686	73.9	73	0.947
(MIN, MAX)		(50,100)	(50,95)		(50, 100)	(55,95)	
Sex	**Men**	**6**	**11**	0.089	**6**	**8**	**0.053**
	Women	**12**	**5**		**11**	**3**	
Smoking	**Yes**	1	1	0.632	1	1	0.578
	No	16	15		15	10	
	NA	1	0		1	0	
Stage	**0**	1	3	0.385	1	2	0.315
	1	3	4		3	4	
	2	9	4		8	2	
	3	5	5		5	3	
T Staging	**T0**	1	3	0.257	1	2	0.187
	T1	0	2		0	2	
	T2	3	2		3	2	
	T3	14	9		13	5	
Lymph Node Involvement	**N0**	13	11	0.845	12	8	0.595
	N1	4	5		3	3	
	N2	1	0		1	0	
Tumor location	**Colon**	8	5	0.332	7	2	0.249
	Rectum	10	11		10	9	
Surgery Type	**Left**	5	3	0.795	4	1	0.519
	Right	3	2		3	1	
	Rectum	10	11		10	9	
Pre-Op NACRT	**Yes**	8	7	0.968	8	6	0.699
	No	10	9		9	5	
Adjuvant treatment	**Yes**	12	7	0.179	12	4	0.121
	No	6	9		5	7	
Drug Compliance	**Average Intake**	91.56%	74.8%	0.103	96.76%	86.67%	0.205
	Drug Non-Compliance rate	1[a]/18	5[b]/16	0.078	0[c]/17	0/11	PC

Table 1: Baseline demographic and clinical characteristics of: (i) all 34 randomized patients, and (ii) 28 protocol compliant patients. **a -** one patient was withdrawn prior to surgery due to pre-surgical metastasis and treatment was not initiated; **b** – 5 patients are excluded from the protocol compliant group. 4 were not drug compliant, and one patient in which metastases were found at surgery continued taking the drug treatment and was 100% drug compliant and was included in the safety analyses, **c**- Drug-intake records from treatment stages 3&4 are missing for one patient in the placebo group. In all analyses, this patient is regarded as drug-compliant. **PC** – All patient in the PC group were protocol compliant.

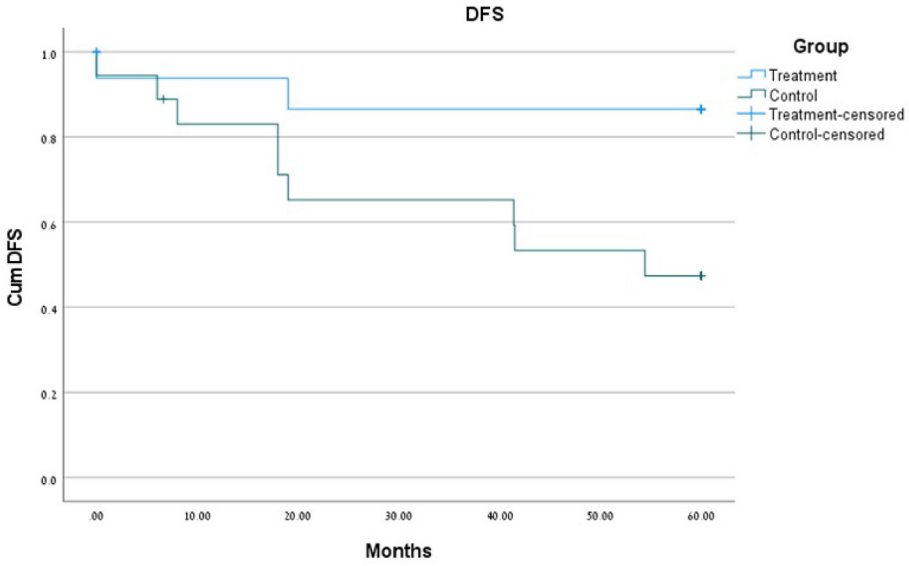

Fig. 2. Intent-to-treat analysis, 5-year DFS.
Fig. 2: Intent-to-treat analysis. Kaplan-Meier curves for 5-year DFS in the treatment and placebo groups. Log-rank test indicated significant group difference (p = 0.033).

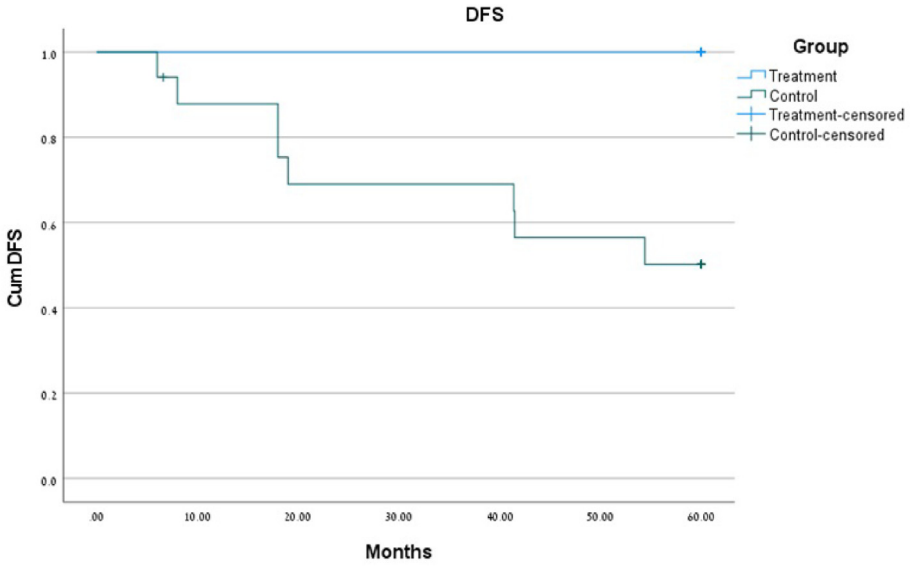

Fig. 3. Protocol compliant analysis, 5-year DFS.
Fig. 3: Protocol compliant analysis. Kaplan-Meier curves for 5-year DFS in the treatment and placebo groups. Log-rank test showed significant group difference (p = 0.007).

3.4. Safety outcomes

Adverse events rate did not significantly differ between the two groups (Table 2). None of the serious adverse events or surgical complications were called by the investigators as related to the drug treatment. Two patients suffered from asymptomatic bradycardia which required omission of doses until resolution of the bradycardia according to the study protocol.

4. Discussion

In this pilot randomized-controlled COMPIT trial, 20-day perioperative treatment with propranolol and etodolac significantly increased 5-year disease-free survival rate compared to a placebo control treatment. Among both protocol compliant and intent-to-treat patients, 0/11 and 2/16 (respectively) exhibited recurrence during the 5-year follow-up, compared to 8/17 and 9/18 control patients. Overall survival rates showed similar favorable trends for the treated groups, but did not reach statistical significance, which is expected given the small number of events. This is the first randomized controlled trial identifying long-term clinical benefits of a combined perioperative blockade of inflammation and adrenergic signaling in CRC patients undergoing surgery with curative intent. Other clinical trials have reported beneficial effects on short-term biomarkers, employing either propranolol alone [18,19] or propranolol and etodolac [14,15,20] (for reviews see: Eckerling

Table 2
Safety data.

	Table 2: Safety data[a] for (i) all 34 randomized patients, (ii) 28 Protocol-compliant patients					
	Intent-to-Treat (N = 34)		p-val	Protocol-Compliant Patients (N = 28)		P-val
	Placebo (n = 18)	Drugs (n = 16)		Placebo (n = 17)	Drugs (n = 11)	
	Intra-operative Complications					
No. of intra-operative Complications	1/18	0/16	0.99	1/17	0/11	0.99
	Potentially drug-related adverse events during the intervention phase of the study (5 days before surgery to 14 days after surgery − 20 days)					
Event type						
No events	17	13	0.393	16	8	0.244
Mild	0	0		0	0	
Moderate	1[b]	2[c]		1[b]	2[c]	
Severe	0	1[d]		0	1[d]	
Events per Patient						
0	17	13	0.529	16	8	0.275
1	0	2[c]		0	2[c]	
2	1[b]	1[d]		1[b]	1[d]	
	Post-surgical Complication (Up-to 30 days post-surgery)					
No. of Events per Patient						
0	**13**	**10**	0.566	**12**	**6**	0.499
1	**4**	**2**		**4**	**2**	
2	**1**	**2**		**1**	**1**	
3	**0**	**1**		**0**	**1**	
4	**0**	**0**		**0**	**0**	
5	**0**	**1**		**0**	**1**	

Safety data for (i) all 34 randomized patients, and (ii) 28 protocol-compliant patients.
[a] All of the mentioned event are Non-Serious AEs.
[b] One patient suffering from breathing difficulties and atelectasis.
[c] Bradycardia,
[d] One patient suffering from pulmonary edema and low-blood pressure, mandating treatment cessation.

et al., 2021 [21])

The randomized placebo-controlled trial design of this study is a major strength. However, the results should be interpreted with caution due to several limitations. First, the small sample size recruited in a single center limits the ability to generalize the findings. Power analysis was made to detect differences in biomarkers, which have shown significant favorable impacts [10], including reduced EMT and other molecular indices in the excised tumor. Following these encouraging results, we herein studied clinical outcomes of a five-year follow-up. The small sample size limits statistical power for detecting *a priori* group differences, and precludes the use of multivariate analyses to control for potential confounders such as gender distribution and cancer stage. Notably, ancillary analyses showed that beneficial effects were maintained within each sub-category of these variables, as indicated in the results section (i.e., within each sex and tumor stage). Also, existing literature finds men to show similar or poorer outcomes than women [22,23] (which is thus expected to strengthen, rather than weaken, the findings). Notably, pre-operative stratification based on disease stage is not possible in CRC even in future larger studies, as staging is determined by pathologic assessment of the resected specimen, and we assume that with larger sample size the disease stage will be more evenly distributed.

It is also worthy to note that the use of the combined drug treatment has both strengths and limitations. Translational studies have shown significant synergism between the beneficial effects of the drugs, such that each drug alone often had only minimal benefits. For example, in two studies employing B16 melanoma and CT26 hepatic cancer models, the use of each drug along had null effects, while combined use significantly improved survival (B16 model) [24], and reduced the number of metastases (CT26 model) [25]. On the other hand, in the clinical setting the combined use excludes approximately 50% of patients from being eligible for the study, due to medical contra indications for the use of either of the study medications or the chronic use of any beta-blocker or COX-inhibitor (based on our experience in 2 completed clinical trials in breast [14,20] and colorectal [15] cancers, and on 2 on-going trials in pancreatic and colorectal cancers). This limit the generalizability of the results and pose a practical challenge to recruitment. Future studies should also test each drug alone, and/or substitutions to each of the drugs.

Five-year DFS rates for CRC patients vary between ~50% and ~75%, depending on disease stage and location [8,26–29], among other factors. In the current study, 5-year DFS in the placebo group was 50%. The effect size of the treatment was large, with a recurrence rate of only 12.5% in the drug-treated intent-to-treat analysis, and 0%, in the protocol-compliant patients. Given the small sample size of this study, this large effect size is inadequate to provide a good estimation for population effect size. However, the statistical significance evident in DFS rates suggest that this positive effect is unlikely to occur by chance. Systemic oncological treatments are currently given for the gain of much smaller effect sizes than the one showed in this study [23,30]. Thus, well-powered studies assessing the use of perioperative COX-2 inhibitors and beta-blockers are worthwhile even if the actual effect size is much smaller than that observed herein.

Notably, most of the currently available anti-metastatic treatments cannot be used in the perioperative period, owing to their detrimental effects on wound healing, and/or other contraindications to surgery. Indeed, safety concerns have been raised regarding the use of NSAIDs and/or beta-blockers in the perioperative context. Specifically, the perioperative use of the beta-1 antagonist metoprolol, but not non-selective beta-antagonists (such as propranolol), were associated in some studies with increased risk for post-operative myocardial infraction, stroke, and death [31,32]. This led to recommendations by the American Heart Association (AHA) [33] and the European Society of Cardiologists (ESC) [34] to initiate beta-blockers treatment at least two days before surgery in titration, as is conducted herein. Concerns were also raised regarding the perioperative use of COX-inhibitors and potential increased risk for cardiovascular events, bone, and tissue healing, yet Enhanced Recovery After Surgery (ERAS) Society protocols state that current evidence does not justify avoidance of NSAIDs' perioperative use in patients with low cardiovascular risk [35]. Moreover, several studies found that the specific use of COX-2 inhibitors in the perioperative period did not cause an increase in renal, cardiac or thrombotic adverse events [36–38]. A concern has been raised that using NSAIDS in the perioperative period may increase the risk of anastomotic leakage, but these studies included non-selective NSAIDS such as Diclofenac [39]. In contrast, a recent study with colorectal cancer patients, suggest that post-operative use of non-selective COX-inhibitors might confer some protective effects against anastomotic leakage [40]. Furthermore, in the current study ($n = 34$) [15], in a previous study in breast cancer patients (38) [14], and in two ongoing clinical trials in CRC ($n = 28$) and in pancreatic cancer patients ($n = 18$) (unpublished data), all of which employ the same combination of propranolol and etodolac starting 5 days before surgery, there were no differences in adverse event rates between the intervention and the placebo groups (in each study separately, and when combined). Taken together, the treatment seems to be safe for perioperative treatment when employing current exclusion (for extended safety discussion see Ricon et al., 2019 [41]).

5. Conclusions

The results of this pilot study suggest that pharmacological suppression of adrenergic and inflammatory signaling is readily feasible using re-purposed safe and available marketed drugs, and may significantly reduce the risk for post-surgical CRC recurrence. These results underscore the need and scientific justification for larger studies. Importantly, pharmaceutical companies have little incentive to conduct clinical studies employing off-patented drugs (such as etodolac and propranolol), so the impetus for such studies will need to come from researchers, practitioners, and patient advocacy groups. Currently, we are testing the perioperative use of beta-blockers and COX-2 inhibitors in another cohort of CRC patients, hoping to recruit a larger sample (NCT03919461). We welcome potential collaborations in this regard.

CRediT authorship contribution statement

Itay Ricon-Becker: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **Rita Haldar:** Data curation, Methodology, Validation, Writing – review & editing. **Maytal Shabat Simon:** Data curation, Investigation, Methodology, Writing – review & editing. **Mordechai Gutman:** Conceptualization, Investigation, Project administration, Writing – review & editing. **Steve W. Cole:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Shagmar Ben-Eliyahu:** Conceptualization, Formal analysis, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing. **Oded Zmora:** Conceptualization, Formal analysis, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.10.013.

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