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Bladder Cancer

Effect of a Smoking and Alcohol Cessation Intervention Initiated Shortly Before Radical Cystectomy—the STOP-OP Study: A Randomised Clinical Trial

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Article info

Abstract

Background: Evidence concerning the reduction of postoperative complications due to smoking and alcohol drinking in patients undergoing radical cystectomy is incomplete.

Objective: To evaluate the efficacy of a 6-wk smoking and/or alcohol cessation intervention, initiated shortly before surgery and continued until 4 wk after, in reducing complications.

Design, setting, and participants: Between 2014 and 2018, we enrolled 104 patients with high-risk bladder cancer who were daily smokers or consuming at least 3 units of alcohol daily in a multicentre randomised clinical trial.

Intervention: Patients were randomised to a 6-wk intensive smoking and/or alcohol cessation intervention or treatment as usual.

Outcome measurements and statistical analysis: The primary endpoint was the number of patients developing any postoperative complication, or death, within 30 d after surgery. The secondary endpoints were successful quitters, health-related quality of life, length of stay, time back to habitual activity, and mortality. An intention-to-treat analysis was applied to evaluate treatment effect.

Results and limitations: There were some differences in baseline demographic and lifestyle characteristics. Postoperatively, 64% in the intervention group versus 70% in the control group (risk ratio [RR] 0.91, confidence interval [CI] 0.68–1.21, $p = 0.51$) developed complications. Significantly fewer patients developed three or more complications after 30 d (RR 0.39; CI 0.18–0.84, $p = 0.01$). The rates of successful quitting were 51% in the intervention group and 27% in the control group (RR 2, CI 1.14–3.51, $p = 0.01$). The

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external validity of this trial may be limited because 53% of eligible patients refused participation.

Conclusions: Despite a significant effect on the quit rate at completion of the intervention, this multimodal prehabilitation did not show a significant difference regarding our primary outcome postoperative complications.

Patient summary: A 6-wk smoking and alcohol cessation intervention in relation to bladder cancer surgery did not reduce postoperative complications, but it was effective in supporting people to quit in the short term.

1. Introduction

Bladder cancer is seen more frequently in older individuals and is strongly linked to smoking exposure. Radical cystectomy (RC) with pelvic lymphadenectomy and urinary diversion is the standard surgical treatment for muscle-invasive bladder cancer and recurrent high-risk non–muscle-invasive bladder cancer. RC is a complex surgical procedure with a complication rate between 30% and 64% [1], independent of surgical technique [2] and Enhanced Recovery After Surgery (ERAS) programmes [3], indicating that RC in a comorbid population carries significant risks. Evidence on the effect of modifiable lifestyle factors such as smoking and alcohol drinking is sparse [4]. One study indicates that smoking cessation during the first 6 wk after acute surgery also reduces the risk of postoperative complications [5]. Smoking and alcohol consumption are associated with an increased risk of general postoperative morbidity, general infections, wound complications, pulmonary complications, prolonged stay at the hospital, and admission to the intensive care unit [6,7].

It is well known that intensive smoking and alcohol cessation interventions 4–8 wk before surgery reduce the risk of postoperative complications, while preoperative brief interventions with quitting at the day of surgery do not reduce their risk [8,9]. Smoking and risky alcohol drinking are considered preoperative conditioning measures, and even though these have been identified as risk factors for complications after RC [10], there is no available evidence showing whether their correction improves outcomes after RC [3].

Owing to cancer care pathways, patients undergoing major bladder cancer surgery in Denmark have 2 wk for prehabilitation; therefore, the aim of this study was to evaluate the effect of a 6-wk intensive smoking and/or alcohol cessation intervention initiated shortly before RC and continued until 4 wk after surgery on postoperative complications in the short and longer term.

2. Patients and methods

2.1. Patients

Patients from the outpatient clinics (18 yr of age or older) were screened by their designated urologist the day they were scheduled for RC and referred to the local study nurse, who recruited eligible patients face to face. The inclusion criteria were patients scheduled for RC for bladder cancer and who smoked daily and/or consumed at least 3 units of alcohol (36 g) daily. Patients were excluded if they were cognitively unable to provide informed consent; had allergy to disulfiram, benzodiazepines,

or nicotine replacement therapy (NRT); and were pregnant or breastfeeding. Our aim was to reject or confirm a reduction from 50% to 25% in the number of patients who developed any postoperative complication [11]. With a type 1 error risk of 5% and a type 2 error risk of 20% (80% power), the required sample size was 55 patients in each group.

2.2. Study design and recruitment

We performed a multicentre randomised clinical trial in four Danish centres performing RC. At each site, we randomised patients 1:1 to the intervention or the control arm using a computer-generated stratified, block randomisation scheme. Block sizes varied from 2 to 8, and stratification took place for trial site and smoking or risky alcohol drinking or both. We secured the allocation concealment as the randomisation process was part of the electronic case report file, and assignment to intervention or control group was displayed on the computer screen. Study nurses enrolled eligible patients, provided the intervention, and collected data. Owing to the nature of the intervention, patient and study personnel were not blinded, while outcome assessors were blinded to the allocation. All patients signed informed consent before randomisation. We registered the trial before starting inclusion with ClinicalTrials.gov (NCT02188446) and followed the Consolidated Standards of Reporting Trials reporting guideline [12].

2.3. Standard arm

Patients underwent open or robot-assisted RC with pelvic lymph node dissection and urinary diversion, with specific type selected by mutual agreement between the patient and surgeon. All patients followed a clinical care pathway that included general ERAS principles [3], with minor local differences regarding precystectomy prehabilitation defined as nutritional support, enhanced mobilisation, referral to smoking cessation, and preparation for stoma care. Everyone received the national folders on alcohol and tobacco and surgery with written information about the risks of smoking and drinking in relation to surgery. Patients were encouraged to stop smoking and alcohol drinking, and ensured that they were free to access smoking- and/or alcohol-cessation support services in the hospital or elsewhere.

2.4. Intervention arm

Patients in the intervention group received the care described in the standard arm and, in addition, five counselling sessions starting the day the patient was scheduled for RC and continuing after surgery with trained smoking- and alcohol-cessation counsellors following the principles of the gold standard programme (GSP; Supplementary Table 1) [13]. We offered NRT and chlordiazepoxide free of charge to manage withdrawal symptoms. Patients in the alcohol intervention group were also offered low-dose disulfiram to support quitting alcohol drinking. At each visit, patients were asked whether they experienced any adverse events

related to the support medication. Patients were asked to decide a stop-date as soon as possible and not later than the day before surgery. The intervention has been described in detail elsewhere [14].

2.5. Assessment of outcome

The primary outcome was the number of patients who developed any postoperative complication, or death, within 30 d after surgery. At each follow-up visit, patients were asked whether they experienced any complication or they had been prescribed any new drugs. Complications were registered in the medical record system when diagnosed, and two urologists who were not otherwise involved in the study assessed complications through review of the medical record system. We defined complications in accordance with European Association of Urology guidelines [15] as any deviation from the ideal postoperative course that is not inherent in the procedure and does not comprise a failure to cure. We used predefined definitions of complications (Supplementary Table 2).

Secondary outcomes were the types and grades of complications within 30 and 90 d after surgery assessed using the Clavien-Dindo classification [16]. Smoking cessation and alcohol cessation up to 12 mo postoperatively were both self-reported and verified with biomarkers. In accordance with the literature, CO cut-off for smoking abstinence was set at 4 ppm [17]. Successful quitting of alcohol drinking was defined as no alcohol drinking at all till the end of intervention and thereafter according to the national guidelines (maximum 7/14 units of alcohol weekly for women/men). Alcohol markers were phosphatidylethanol in blood [18] and ethyl glucuronide in urine [19]. Mortality up to 12 mo, length of stay (LoS), time to return to work or habitual level of activity, and health-related quality of life (HRQoL) up to 12 mo postoperatively were evaluated. We assessed HRQoL with EQ-5D, a generic quality of life instrument that comprises five dimensions [20].

2.6. Statistical analysis

We reported variables as medians with ranges for continuous variables and counts with percentages for categorical variables. Comparisons between groups were performed by independent two-sample t tests, if normality assumption could be assumed; otherwise, Wilcoxon sum-rank test was used. Chi-square test was used for categorical variables, and for observations with a count of <5, Fisher's exact test was used. We evaluated normality assumptions for continuous variables by QQ plots. Risk ratio (RR) between the intervention and control groups were calculated for complication outcomes and abstinence, and tested for independence of exposure by normal approximation. We considered effects statistically significant if p values were <0.05. All analyses was performed using R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient population

Between November 20, 2014, and July 27, 2018, 104 patients (95% of the estimated sample size) were randomly assigned to two groups: 52 to the intensive smoking and alcohol cessation intervention group and 52 to the standard care group (Fig. 1). We terminated inclusion of patients in July 2018 before the estimated number was met, since recruitment was slowing down. In median, the inclusion and thereby the intervention were started 8 d before RC (range 1–55). Compliance with meetings in the intervention group was high: all patients except for two attended all five meetings. One missed one meeting for unknown reasons,

and one missed two meetings because the patient was admitted to the intensive care unit. Of the 104 patients who were randomly assigned, eight did not have surgery and two withdrew consent shortly after randomisation. Thus, 47 patients in the intervention group and 47 in the control group were included in the intention-to-treat analysis. There were some differences in baseline demographic and lifestyle characteristics (Table 1), with more women in the control group and more patients having undergone neoadjuvant chemotherapy in the intervention group. Patients were followed up for 12 mo.

3.2. Complications

After 30 d, 30 patients in the intervention group developed one or more postoperative complications compared with 33 patients in the standard care group (RR 0.91, confidence interval [CI] 0.68–1.21, $p = 0.51$). Six patients in each group had reoperations.

Type of complication differed between groups, with the largest difference seen in gastrointestinal complications at 30 d (RR 0.48, CI 0.25–0.90, $p = 0.02$) and 90 d (RR 0.43, CI 0.23–0.81, $p = 0.005$; Fig. 2). When looking at the severity of the complications according to the Clavien-Dindo classification, minor complications (grade 1–2) were seen in 27 patients in the intervention group and in 30 patients in the control group at 30 d (RR 0.90, CI 0.65–1.25, $p = 0.53$). Major complications (grade 3–5) were seen in 11 and 15 patients, respectively (RR 0.73, CI 0.38–1.43, $p = 0.36$; Fig. 3). One patient in each group died within 90 d due to complications. After 12 mo, the mortality rate was similar between groups (Table 2) and in all cases; mortality after 90 d was due to disease recurrence. We found that the number of patients with three or more complications was seven in the intervention group and 18 in the control group (RR 0.39; CI 0.18–0.84, $p = 0.02$) at 30 d, and seven and 20, respectively, at 90 d (RR 0.35, CI 0.16–0.75, $p = 0.003$). Six patients in each group had reoperations (RR 1, CI 0.35–2.88, $p = 1.00$) and 19 patients in the intervention group compared with 28 in the control group (RR 0.68, CI 0.45–1.03, $p = 0.06$) had unplanned visits at 90 d.

3.3. Secondary outcomes

The LoS was 7 d in both groups (range 3–61 in the intervention group vs 3–80 in the control group, $p = 0.06$). After the completion of the intervention, 24 patients (51%) in the intervention group compared with 12 patients (27%) in the control group were abstinent (RR 2 [1.14–3.51], $p = 0.01$). The median time from quitting to surgery was 2 d (interquartile range 1–8; Supplementary Fig. 1). At 12-mo follow-up, seven patients in the intervention group versus ten ($p = 0.32$) in the control group were continuously smoke free or had reduced alcohol intake according to national recommendations.

After 30 d, four patients in each group had returned to work or habitual level of activity ($p = 1$), and after 12 mo, 13 patients in the intervention group compared with 19 in the control group had still not returned to work or habitual level of activity ($p = 0.53$; Supplementary Fig. 2). HRQoL was similar between groups at the completion of the intervention (0.8; range 0.5–1 in the intervention group and 0.4–1 in the control group, $p = 0.16$) and after 12 mo (1 in the
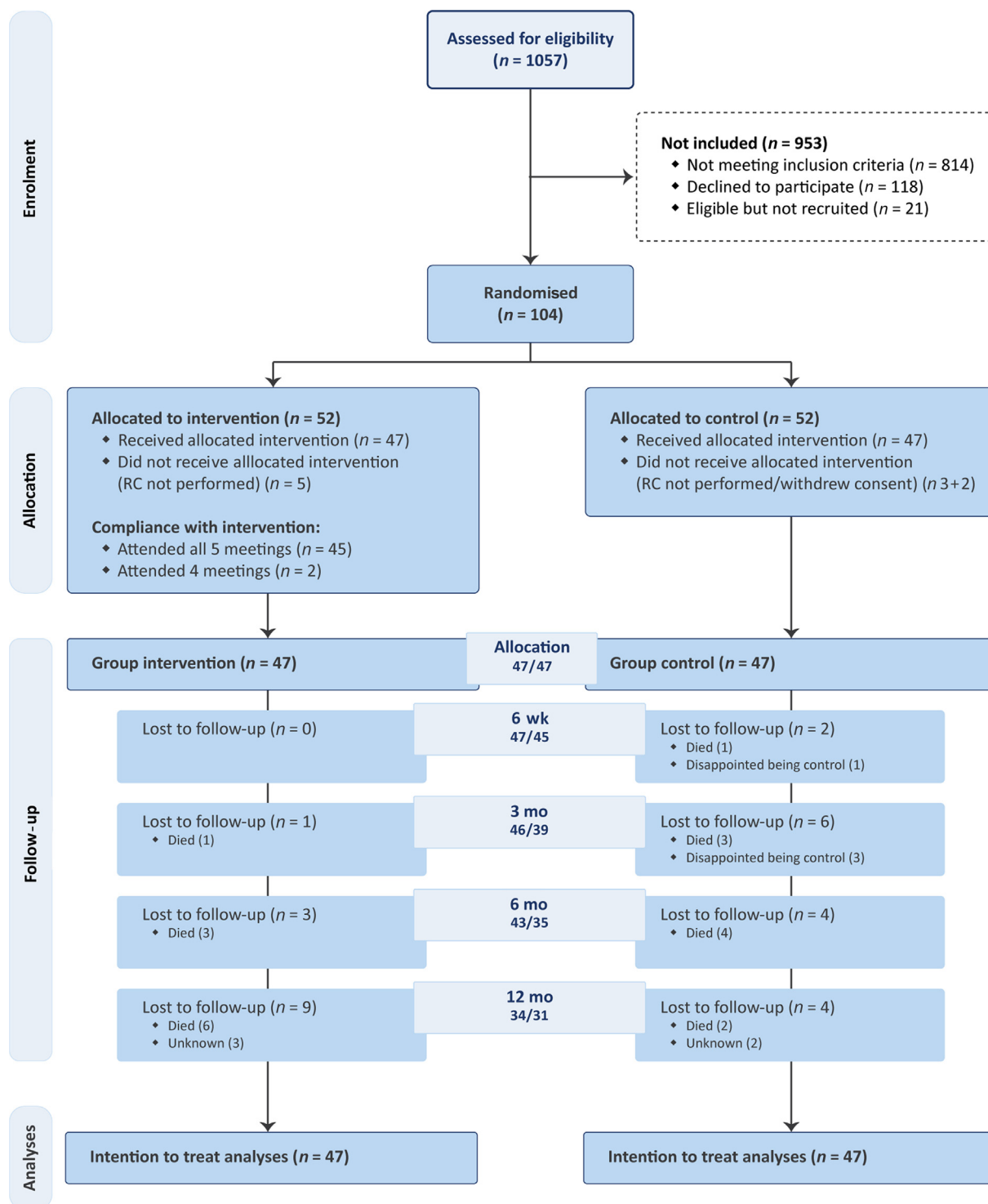
Fig. 1 – Patient trial profile. RC = radical cystectomy.

intervention group [range 0.5–1] vs 0.9 in the control group [range 0.4–1], p =0.25; Table 3 and Supplementary Fig. 3).

3.4. Adverse events

No patients reported any adverse events related to the use of the study medication.

4. Discussion

Despite a significant effect on successful quitting in the short term, we did not find any difference in postoperative complications, except that we found significantly fewer patients with three or more complications in the intervention group. This favour of the intervention group may reflect

Table 1 – Baseline characteristics of the 2 × 47 patients.

	Intervention arm (n = 47)	Control arm (n = 47)
Preoperative factors		
Age	63 (43–82)	68 (48–81)
Men	41 (87%)	31 (66%)
Living alone	23(49%)	19 (40%)
Education short level [a]	15 (33%)	12 (26%)
HRQoL (EQ-5D)	0.8 (0.5–1)	0.8 (0.6–1)
Lifestyle habits		
Body mass index (kg/m^2)	25 (17–36)	25 (15–41)
BMI ≥30	6 (13%)	6 (13%)
Malnutrition (stress metabolic grade 3)	4 (9%)	1 (2%)
Physical activity <30 min/d	14 (30%)	19 (40%)
AUDIT-C for men	5 (0–12)	6 (0–11)
AUDIT-C for women	5 (1–6)	2 (0–5)
Timeline follow-back units per week [b]	21 (0–64)	24 (14–38)
Alcohol consumption ≥21 units/wk	7 (15%)	9(20%)
Smokers: pack years [b,c]	39 (2–96)	39 (1–83)
Pack years (all)	36 (17–96)	44 (2–83)
Cigarettes per day	17 (2–40)	17 (1–30)
Fagerströms score	4 (0–7)	4 (0–8)
History of disease		
Clinical and TURBT stage	Tis: 2 (4%)	Tis: 1 (2%)
	T$_1$: 14 (30%)	T$_1$: 17 (36%)
	T$_2$: 21 (45%)	T$_2$: 13 (28%)
	T$_3$: 9 (19%)	T$_3$: 12 (26%)
	T$_4$: 1 (2%)	T$_4$: 4 (8%)
Neoadjuvant chemotherapy	18 (38%)	10 (21%)
Charlson comorbidity index ≥2	17 (36%)	17 (36%)
ASA [d] class 2–3	40 (93%)	36 (92%)
Preoperative laboratory test		
Haemoglobin (g/dl)	7.9 (5.5–9.7)	8.2 (5.8–10.4)
CO breath test (ppm)	6.5 (0–49)	6 (0–29)
FEV$_1$ (l/s)	2.5 (0.4–4.5)	2.2 (0.8–4.5)
PEth (µmol/l)	0.1 (0.005–3)	0.1 (0.005–1)
Intraoperative factors		
Robotic cystectomy	20 (43%)	18 (38%)
Urinary diversion	Ileal conduit 40 (85%)	Ileal conduit 43 (92%)
	Neobladder 5 (11%)	Neobladder 2 (4%)
	Cont. Cut. Reserv 2 (4%)	Cont. Cut Reserv 2 (4%)
Operative time (min) [e]	303 (132–565)	249 (92–413)
Blood loss (ml)	750 (50–3035)	635 (40–2500)
Blood transfusion	4 (9%)	5 (11%)

ASA = American Society of Anesthesiologists; AUDIT-C = alcohol use disorders identification test; BMI = body mass index; FEV$_1$ = forced expiratory volume in 1 s; HRQoL = health-related quality of life; PEth = phosphatidylethanol; TURBT = transurethral resection of a bladder tumour.

The data are presented as number (%) or median (range).

Seventy-two patients participated in the smoking group, 12 in the alcohol group, and ten in the combined smoking and alcohol group.

[a] Short education: no education except primary school or short work-related courses.

[b] TLFB measures detailed alcohol information from research participants and clinical populations.

[c] Smoking years × daily consumption/20.

[d] ASA classification of physical health.

[e] The time from incision to closure. Data were available for 29 patients in the intervention group and 32 in the control group because of change from paper medical record to an electronic medical record.

the difference in the number of complications per patient. To our knowledge, this is the first study to evaluate this with a randomised design in patients undergoing RC. However, several observational studies have identified smoking as a predictor of complications following RC [21–24] and thereby indicated a potential effect of a smoking cessation intervention, but no previous studies have targeted smoking and risky alcohol intake in this patient group.

The lack of an effect on postoperative complications could be explained by the timing of intervention, which for the large majority in the intervention group was <10 d prior to surgery as well as an even shorter period of abstinence (median 2 d). Some improvement of pathophysiological mechanisms such as nicotine metabolism and alcohol-induced imbalance of coagulation could take place within a short time, while most require a longer time [25], suggesting that the participants should have stayed abstinent for a longer period preoperatively [8,9]. Reducing the delay of the start of intervention to the quit day could also add to a better outcome.

The quit rate in the intervention group was comparable with that in other studies investigating intensive smoking or alcohol cessation interventions [26,27]. We chose the intensive intervention for smoking and alcohol cessation with repeated contact with the counsellor and pharmacological support, because it is the only evidence-based intervention and has been proved to be more effective than shorter interventions [8,13]. Interestingly, more people than anticipated in our control group quit after the detailed patient information and the national folder including advice to quit , thereby diminishing the treatment difference observed. Long-term abstinence is a continued challenge reflecting that nicotine and ethanol are determinants of addiction; in our study, 21% in the intervention group and 36% in the control group were abstinent after 1 yr. To know whether the health benefits of smoking cessation and alcohol reduction in the long term are substantial both to the individual and to the health costs, further studies on modifiable lifestyle risk factors are needed.

EQ-5D may not be sensitive to identify small changes in HRQoL; this may explain why HRQoL was similar between groups. Time back to work or habitual activity, LoS, and mortality rates were also similar between groups, probably because these outcomes are closely related to the complication rate, which was not significantly different between groups.

Randomised smoking and alcohol cessation intervention studies in the surgical population are sparse [8,9], and one study indicated that intensive smoking cessation initiated immediately after acute fracture surgery reduced the risk of postoperative complications [5]. Considering the time frame from bladder cancer diagnosis until surgery, future research should investigate whether an intensive smoking and alcohol cessation intervention starting at least 2 wk prior to surgery can reduce the risk of postoperative complications, which is part of new protocols among patients with cancer ([28], NCT04088968).

A strength of our study is the high compliance with the intervention, indicating that those enrolled in the study found the intervention meaningful. This is supported by a qualitative study nested to the randomised controlled trial exploring the barriers and facilitators for participating in the intervention [29]. Besides, we had all counsellors participate in a 3-d course in the GSP.

Another strength is that the two assessors, who recorded all postoperative complications throughout the study

Variable		RR (95% CI)	p-value
Number of patients with complications		0.91 (0.68 : 1.21)	0.51
Number of patients with> 3 complications		0.39 (0.18 : 0.84)	0.01
Reoperation		1.00 (0.35 : 2.88)	1
Complication types observed after randomisation arm			
Gastrointestinal		0.48 (0.25 : 0.90)	0.02
Cardiac		0.50 (0.13 : 1.88)	0.30
Infections		0.94 (0.56 : 1.60)	0.83
Wounds		0.64 (0.31 : 1.34)	0.23
Genitourinary		0.71 (0.24 : 2.09)	0.54
Pulmonary		2.00 (0.19 : 21.31)	0.56
Bleeding		0.82 (0.37 : 1.79)	0.62
Miscellaneous		0.64 (0.27 : 1.50)	0.30
Grade of most severe complication (Clavien-Dindo Classification)			
Grade I		1.89 (0.86 : 4.16)	0.11
Grade II		0.70 (0.31 : 1.57)	0.38
Grade IIIa		0.79 (0.28 : 2.21)	0.65
Grade IIIb		0.79 (0.28 : 2.21)	0.65
Minor		0.90 (0.65 : 1.25)	0.53
Major		0.73 (0.38 : 1.43)	0.36

Intervention better   Control better

0   1   2   3   4   5
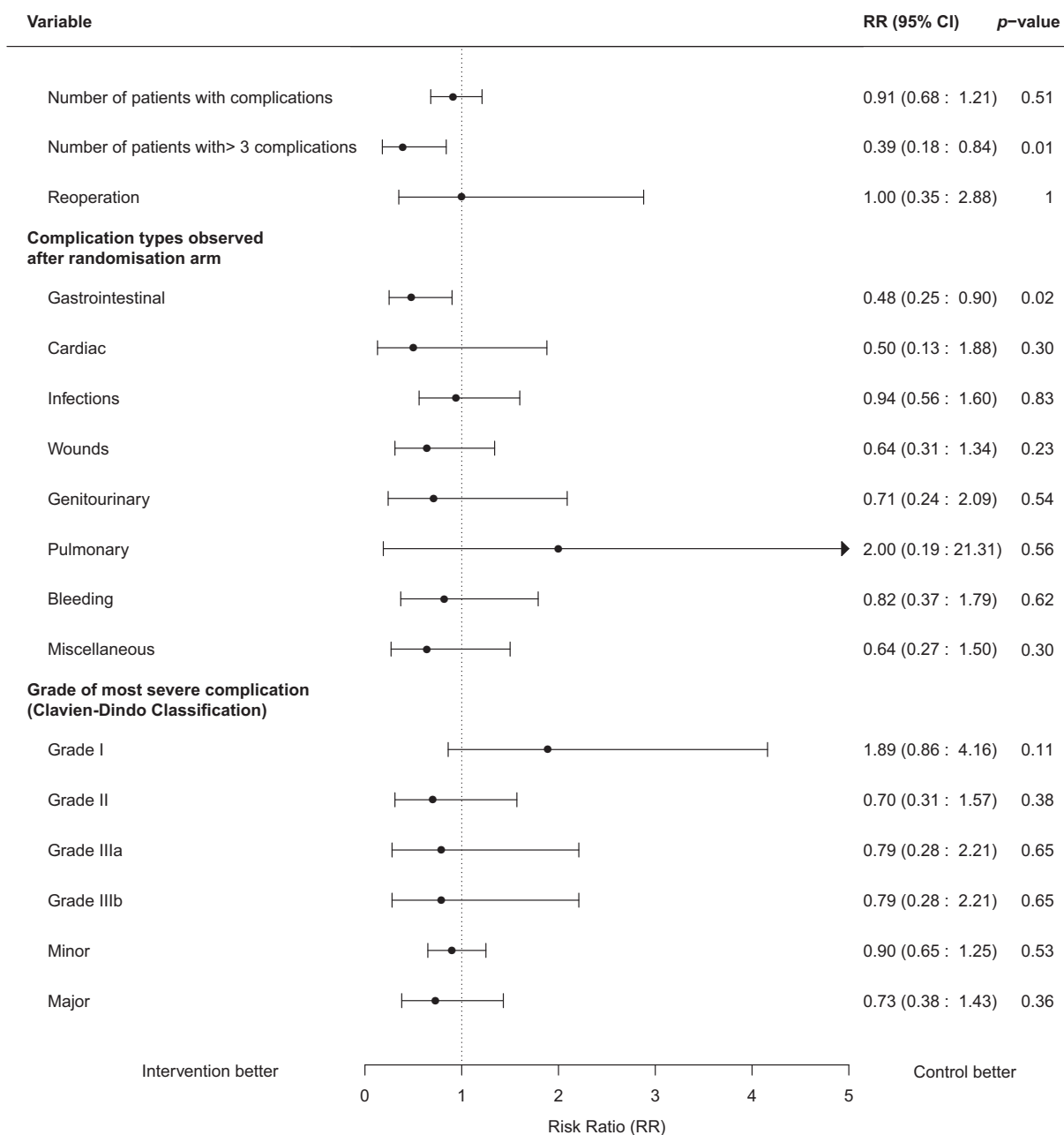
Risk Ratio (RR)

Fig. 2 – Forest plot of 30-d complications. CI = confidence interval; RR = risk ratio.

period using a predefined protocol, were masked to the intervention.

Limitations to our study are related to both external and internal validity. The external validity of this clinical trial may be limited by the large number of patients (53%) who refused to participate in the study. The main reason given was "I want to quit on my own". Previous studies report widely varying participation rates in preoperative smoking cessation interventions ranging from 31% to 96% [8], pointing out the importance to look into strategies to make lifestyle changes in relation to surgery more attractive. Likewise, the external validity is limited by the trial being conducted in centres following ERAS protocols, meaning that our results are generalisable only to centres with similar care protocols. The internal validity may be limited by some differences in the baseline characteristics, but some of them may balance each other. The risk of performance bias was high because blinding of participants and counsellors was not possible due to the nature of the intervention.

Attrition was acceptable, with 14 and 16 patients lost to follow-up in the intervention and control groups, respectively. Four patients were disappointed with being in the control group, five patients were lost to follow-up for unknown reasons at 12 mo, and 20 patients died.
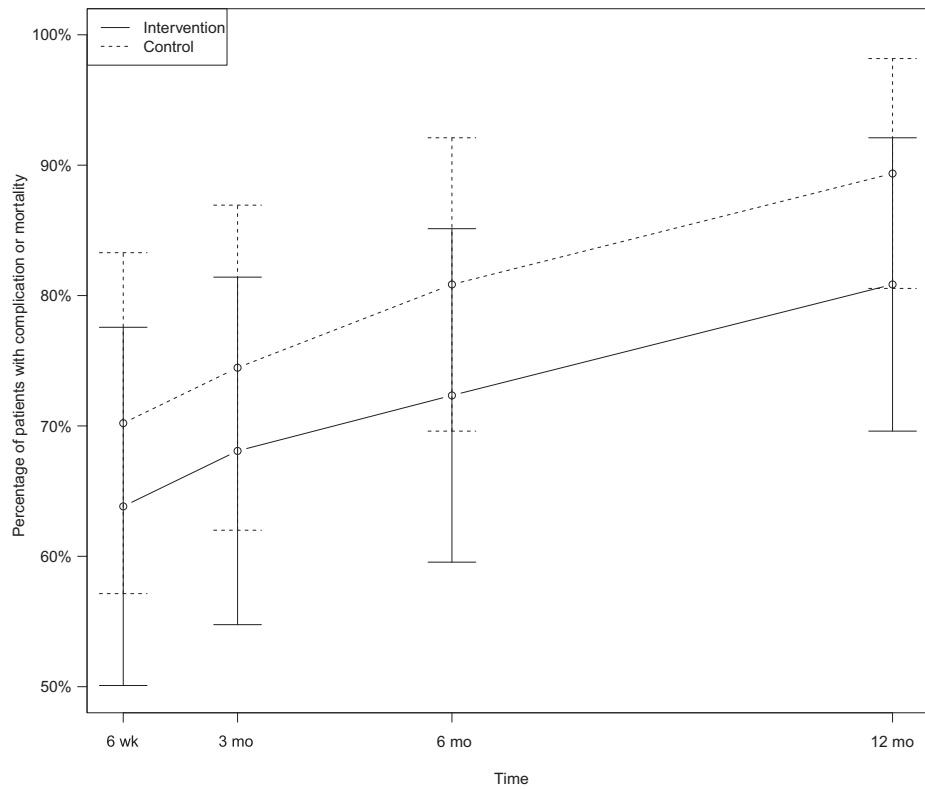
Fig. 3 – Cumulative percentage of patients with complications or those who died within 12 mo postoperatively, with 95% confidence intervals (CIs).

Table 2 – Postoperative complications (cumulative) in 2 × 47 patients including types of complications.

	30 d		90 d	
	Intervention	Control	Intervention	Control
Number of patients with complications (%)	30 (64)	33 (70)	32 (68)	35 (75)
Complication types observed after randomisation arm, no. of patients (%)				
Gastrointestinal	10 (21)	21 (45)	10 (21)	23 (49)
Cardiac	3 (6)	6 (13)	3 (6)	7 (15)
Thromboembolic	0 (0)	0 (0)	0 (0)	0 (0)
Infections	17 (36)	18 (38)	18 (38)	20 (43)
Wounds	9 (19)	14 (30)	9 (19)	14 (30)
Genitourinary	5 (11)	7 (15)	8 (17)	11 (23%)
Pulmonary	2 (4)	1 (2)	4 (9)	1 (2)
Bleeding	9 (19)	11 (23)	9 (19)	12 (26)
Neurological	0 (0)	2 (4)	0 (0)	3 (6)
Procedural	0 (0)	1(2)	0 (0)	1 (2)
Miscellaneous [a]	7 (15)	11 (23)	7 (15)	16 (34)

* Significant result.

[a] Miscellaneous: acidosis, pressure ulcer, and lymphocele.

Table 3 – Secondary outcomes from 2 × 47 patients.

Outcome	30 d			12 mo		
	Intervention	Control	*p* value	Intervention	Control	*p* value
Successful quitters (all) [a], *n* (%)	24 (51)	12 (27)	0.01 *	7 (21)	11 (36)	0.32
Length of stay	7 (3–61)	7 (3–80)	0.06	–	–	–
HRQoL (EQ-5D)	0.8 (0.5–1)	0.8 (0.4–1)	0.20	1.0 (0.5–1.0)	0.9 (0.4–1.0)	0.25
HRQoL (EQ-5D VAS)	74 (0–100)	73 (20–100)	0.070	90 (4–100)	80 (10–100)	0.50
Return to work/habitual activity, *n* (%)	4 (9)	4 (9)	1	22 (71)	18 (60)	0.53

HRQoL = health-related quality of life; VAS = visual analogue scale.
* Significant result.
[a] Successful quitter was defined as not a single puff and zero alcohol drinking after the end of intervention. After 90 d, successful quitting for the alcohol cessation intervention was defined following national guidelines (maximum 7/14 units weekly for women/men).

5. Conclusions

This prospective randomised trial did not detect a beneficial effect of an intensive smoking and/or alcohol cessation intervention compared with standard care regarding overall postoperative complications within 30 d. Likewise, HRQoL, time back to work or habitual activity, LoS, and mortality rates were similar between groups. However, abstinence rates were significantly increased in the intervention group at the completion of the intervention.

Author contributions: Susanne Vahr Lauridsen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tønnesen, Thomsen, Thind, Lauridsen.
Acquisition of data: Lauridsen, Poulsen, Jacobsen, Jensen, Behrend, Steffensen.*Analysis and interpretation of data*: Tønnesen, Thomsen, Thind, Lauridsen.
Drafting of the manuscript: Lauridsen.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Kallemose.
Obtaining funding: Tønnesen, Thind, Lauridsen.
Administrative, technical, or material support: Walther, Isaksson.
Supervision: Tønnesen.
Other: None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euf.2022.02.005.

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