PhD Thesis by Susanne Vahr Lauridsen

Research and Best Practice

Perioperative smoking and alcohol cessation intervention in radical cystectomy: Cessation, complications and patient perspectives.

This thesis has been submitted to the Graduate School of
The Faculty of Health and Medical Sciences,
University of Copenhagen.


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PhD Thesis

Susanne Vahr Lauridsen

Perioperative smoking and alcohol cessation intervention in radical cystectomy

Cessation, complications and patient perspectives

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List of abbreviations

STOP-OP: STOP smoking and drinking alcohol before Operation
RCT: Randomised controlled trial
EAU: European Association of Urology
UBC: Urothelial bladder cancer
RC: Radical cystectomy
ASR: Age standardised rate
TUR-B: Transurethral resection of the bladder
NMIBC: Non-muscle invasive bladder cancers
MIBC: Muscle invasive bladder cancers
ASA: American Society of Anesthesiologists
HRQoL: Health related quality of life
DaBlaCa: Danish Bladder Cancer Group
RARC: Robot assisted radical cystectomy
ORC: Open radical cystectomy
RR: Relative risk
OR: Odd Ratio
CI: Confidence Interval
MD: Mean Difference
ITT: Intention to treat
NRT: Nicotine replacement therapy
CO: Carbon monoxide
VAS: Visual analogue scale
LDLP: Low density lipoprotein
HDLP: High density lipoprotein
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
GRADE: Grading of Recommendations Assessment, Development and Evaluation
CCI: Charlson Comorbidity Index
MSKCC: Memorial Sloan Kettering Cancer Center
GSP: Gold Standard Programme
Papers included

Study I:

Paper I: Published
Lauridsen SV, Tønnesen H, Jensen BT, Neuner B, Thind P, Thomsen T
Complications and health related quality of life after robot-assisted versus open radical cystectomy: a meta-analysis of four RCTs.
Systematic Reviews (2017) 6:150

Study II:

Paper II: Published
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STOP smoking and alcohol drinking before OPeration for bladder cancer (the STOP-OP Study), perioperative smoking and alcohol cessation intervention in relation to radical cystectomy: study protocol for a randomised controlled trial
Trials (2017) 18:329

Paper III: (Manuscript)
Lauridsen SV, Thomsen T, Kallemose T, Thind P, Tønnesen H
Success of a smoking cessation intervention in patients scheduled for radical cystectomy: A randomised controlled trial.

Paper IV: (Manuscript under review)
Lauridsen SV, Thomsen T, Kaldan G, Lydom LN, Tønnesen H
Smoking and alcohol cessation intervention in relation to radical cystectomy: A qualitative study of heavy smokers and risky drinkers’ experiences.
1. Introduction

There are many risk factors in surgery and some like smoking and excessive alcohol intake are preventable. Thus, existing evidence shows that the increased risk of postoperative complications is significantly reduced to approximately half after a 4- to 8-week intensive preoperative, face-to-face lifestyle intervention programme [3, 4]. Until now no studies have evaluated the effect of intervention on both smoking and alcohol consumption shortly before and 5 weeks after major surgery.

Although there has been a decline in the number of smokers since the 1950s with 17 % of men and 15 % of women currently smoking daily, 13,600 people die annually from smoking in Denmark [5]. Seven percent of the daily smokers are heavy smokers (> 15 cigarettes daily) [6]. The causal relationship between smoking and diminished overall health, self-reported poor health, increased absenteeism from work, and increased health care utilization and cost is well established [7, 8]. Regarding alcohol consumption in Denmark, 9 % of the population over 15 years of age have a high-risk alcohol intake (> 21/14 drinks per week for men/women) [9]. Alcohol is a component cause for more than 200 diseases [10] and accounts for an estimated 6 % of all deaths [11]. Excessive alcohol consumption leads to 3000 deaths per year in Denmark [9].

Urothelial bladder cancer (UBC) is the fourth and ninth most common cancer in men and women, respectively [12] with an estimated 1800 new cases annually in Denmark [13, 14]. Cigarette smoking increases the risk fivefold for bladder cancer when compared with the risk in non-smokers [15, 16]. No association between alcohol drinking and bladder cancer risk have been identified, even at high levels of consumption [17]. Radical cystectomy (RC) is the gold standard treatment for patients with muscle-invasive bladder cancer and in selected patients with the non-muscle invasive form [18]. Today the postoperative mortality rate is less than 3% at 90 days [19, 20], but RC remain a procedure with significant morbidity [21, 22].

The required cancer pathway in Denmark [23] means patients undergoing RC have a short timeframe before surgery and cannot benefit from existing knowledge resulting from a 6-8 week preoperative intervention. Therefore the aim of this thesis was to evaluate smoking and alcohol cessation and
complications in relation to radical cystectomy, and to explore patients’ experience of a 6 week smoking and alcohol cessation intervention.

2. Background

2.1 Urothelial bladder cancer

Urothelial bladder cancer (UBC) is the ninth most common cancer in the world with an estimated 430,000 new cases diagnosed worldwide in 2012 [12, 24]. In the Western world it is the fourth and ninth most common cancer in men and women, respectively [12].

Denmark has the highest age standardised incidence rate in Northern of Europe (ASR: 27.4 per 100,000). Even though both incidence and mortality rates have stabilised or declined in men in Northern of Europe since the mid 1990’es, the mortality rate remains the highest recorded worldwide [25]. UBC is two-fold higher in first-degree relatives of UBC patients and inherited genetic predispositions may confer additional risks to external exposures of carcinogens such as tobacco smoke, aromatic amines and polycyclic aromatic hydrocarbons [12, 26]. The first epidemiological observations regarding the relationship between tobacco smoking and the development of UBC were published in 1950 and in 1986 it was stated that smoking caused bladder cancer [27] Men are four times more likely to develop UBC than women; which reflects the pattern of tobacco smoking, occupational carcinogen exposure, and lifestyle [15, 16, 28]. Even though men are more likely to develop UBC than women, women present with more advanced disease and have lower survival rates [29]. The reason for this difference is not fully understood, but can partly be explained by women experiencing longer delay in diagnosis from initial haematuria complaint due to differential diagnosis like urinary tract infections being more prevalent than bladder cancer in women [30]. The disease occurs most frequently after 60 years of age [25] and mean age at diagnosis is 67 years [31]. The 5-year recurrence-free survival in patients with ≤ pT2, pN0 is 73 %, while the 5-year recurrence-free survival of patients with positive lymph nodes are 33 % [32]. After radical cystectomy (RC) the recurrence-free survival is 52-58 % independent of surgical technique [33, 34].
About 90% of all cases of UBCs are urothelial cancers, with the remainder consisting of squamous cell carcinoma and adenocarcinoma [24, 26]. Approximately 75% of newly detected cases are classified as non-muscle invasive bladder cancers (NMIBC) with the disease confined to the mucosa (Ta, Carcinoma in situ) or submucosa (T1). About 20% of NMIBC progress to muscle invasive bladder cancer, progressing beyond the mucosa and the submucosa and infiltrating the detrusor muscle (Figure 1) [35] [36].

NMIBC is treated with transurethral resection of the bladder (TUR-B) often followed by intravesical instillations of chemotherapy or immunotherapy [37]. Radical cystectomy with lymph node dissection is the standard treatment for localized UBC; in males RC includes removal of the prostate and the seminal vesicles and in women RC includes removal of the internal female genitalia. In both men and women the urethra is removed if malignancy is identified [36]. RC is recommended to be performed at centres highly experienced in the surgical technique regarding both cystectomy and urinary diversion and also postoperative care of the patient [21, 38, 39]. Therefore, in Denmark, treatment of bladder cancer has
been centralized to five departments that perform about 300 RC operations each year [40]. The cancer pathway in Denmark means that the aim is to treat patients diagnosed with UBC within 2 weeks [23].

RC is a complex and multifaceted surgical procedure with a 90-day mortality rate of approximately 3-6% [36, 41, 42]. Age, ASA classification and Charlson score [43] seem to be independent predictors of 90-day mortality [44]. Postoperative morbidity after RC is frequent despite implementation of fast-track care pathways and robotic-assisted cystectomy [45, 46]. Complication rates vary from 30-64% even in high-volume centres [47] with most complications being diversion related [48]. Common complications include gastrointestinal complications (27-29%), infections (23-25%), and impaired wound healing (5-15%) [47, 49], all of which are burdensome for the individual patient and costly for society. In general, lower morbidity has been observed for high volume surgeons and hospitals, reflecting the importance of experience with RC [50-52]. Inconsistency in reporting of complications has challenged the comparison of surgical outcomes across studies. The need to compare complications in a systematic, objective, and reproducible way has led to the EAU recommendation to use the Clavien –Dindo system [53, 54] when reporting complication after urological surgical procedures [55] (Table 2).

**Table 1: The Clavien-Dindo grading system for classification of severity of surgical complications**

<table>
<thead>
<tr>
<th>Grades</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.</td>
</tr>
<tr>
<td>Grade II</td>
<td>Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.</td>
</tr>
<tr>
<td>Grade III</td>
<td>Requiring surgical, endoscopic or radiological intervention both without and under general anesthesia.</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Life-threatening complication (including CNS complications) requiring IC/ICU-management, single organ dysfunction (including dialysis), multi organ dysfunction</td>
</tr>
<tr>
<td>Grade V</td>
<td>Death of the patient</td>
</tr>
</tbody>
</table>
2.2 Smoking
Tobacco smoking is the major preventable risk factor for developing UBC and causes 50-65 % of male cases and 20-30 % of female ones [56, 57]. The incidence of UBC is directly related to the duration of smoking and the number of cigarettes smoked per day [58]. Continued smoking after RC increases the risk of readmission for an infectious complication compared with the patient population readmitted for a non-infectious complication [59]. The risk of recurrence and cancer related death after RC has likewise been associated with continued smoking [15].

Tobacco smoke is a mixture of more than 5000 chemicals [56]. The composition of cigarettes has changed during the past 50 years, leading to a reduction in tar and nicotine concentrations in cigarette smoke, but also to an apparent increase in the concentration of specific carcinogens, including naphthylamine, a known bladder carcinogen, and tobacco-specific nitrosamines. This might explain why there has been a relatively stable incidence rate of bladder cancer over the past 30 years [56]. The chemical carcinogens can induce direct DNA damage and promote cancer development in the bladder, but the exact mechanism by which smoking induces malignant transformation is still unknown [60]. A recent meta-analysis estimates the relative risk (RR) for UBC to be 3.47 (3.07–3.91) for current smokers, and 2.04 (1.85–2.25) for former smokers [28]. The risk reduction after smoking cessation indicates reversible changes but it takes a long time to lower the risk given that smokers should quit more than 20 years before diagnosis of UBC to benefit from cessation [61].

The World Health Organization estimates that tobacco smoking is the cause of nearly 6 million deaths every year and that another one million die from passive smoking [62], this means that one person dies every 6 seconds from a tobacco-related disease [63]. The major causes of excess mortality among smokers are cancer, respiratory and vascular disease [64].

In Denmark there has been a reduction in daily smokers from 26 % in 2005 to 16 % in 2016 (women 17 % and men 15 %) [6]. Compared to this 30 % of Danish bladder cancer patients are current smokers and 50 % are former smokers [65].
Tobacco smoking causes diseases like cancer, cardiovascular and pulmonary diseases. Carbon monoxide is a toxic gas that inhibits oxygen transport because it displaces oxygen from haemoglobin and hereby reduces the amount of oxygen carried by haemoglobin in the circulation. This promotes tissue ischaemia and disturbs cardiac rhythm [66]. Nitric Oxide (NO) from cigarette smoke impacts the vascular tone and it might play a significant role in the pathogenesis of arteriosclerosis in the same way as it promotes increase in low density lipoprotein (LDLP) and decrease in high-density lipoprotein (HDLP) [67]. Nicotine in tobacco increases blood pressure, heart rate and the peripheral vascular resistance and in a small study it has been shown to impede normalization of blood lipids [68].

Tobacco addiction is a complex disorder involving pharmacological, conditioning, genetics, and social and environmental factors. Nicotine is the primary addictive agent in tobacco, but addiction is not entirely explained by its delivery as there are also non-nicotine characteristics of tobacco and tobacco smoke. This means that nicotine delivered from tobacco is more toxic and addictive than pharmacological nicotine [69]. Nicotine is quickly absorbed in the bloodstream where it triggers the release of neurotransmitters such as dopamine in the brain. Dopamine is part of the reward system and influences the smoker’s mood and positively reinforces the wish to smoke thus making it difficult to stop smoking [69-71]. The mechanism behind it is not fully understood, but multiple components may contribute to different features of nicotine addictive behaviour including sensitization, withdrawal and tolerance, which occur at different times after nicotine exposure [72]. To get the feeling of pleasure from smoking, developing of tolerance to nicotine means that the smoker needs more cigarettes to feel the pleasure and to avoid withdrawal symptoms, this is called the tobacco addiction cycle [69]. It is estimated that about 50 % of the vulnerability to addiction is attributable to genetic factors [73].

Smoking is sustained through conditioning because it forms an association between the current situation and smoking and then it leads to craving upon re-exposure to a context previously associated with smoking [74-76]. Social factors have been identified as playing an important role especially for adolescents; having friends who smoke is a predictive factor for starting smoking [8].
2.3 Alcohol drinking

Just as tobacco smoking has a huge impact on health [8], alcohol consumption kills thousands of people annually [9]. Risky drinking is defined as consuming more than 252 g of alcohol weekly for men (21 units) or 168 g of alcohol weekly for women (14 units) [9]. It is estimated that there are 500,000 risky drinkers in Denmark of whom 200,000 are alcohol dependent [77].

Both drinking pattern and volume play a role for diseases and injuries caused by heavy alcohol drinking (> 60 grams daily) [10]. Common diseases are cancer, and alcohol induced disorders of liver, pancreas and nervous system. In addition heavy drinking affects immune capacity, cardiac function and endocrine stress response [4].

Alcohol abuse is defined as a destructive pattern of alcohol use occurring within a 12-month period, resulting in a behaviour that influences social, occupational or medical conditions. The alcohol abuser controls their alcohol consumption and has not developed tolerance. Alcohol dependence is defined by the individual losing control over alcohol consumption with drinking becoming the dominant focus of life [78], but like tobacco addiction, several factors like genetics, environmental and developmental play a role. Studies have shown an underlying disruption to brain regions that are important for the normal processes of motivation, reward and inhibitory control in addicted individuals [73] and this might explain why some people get addicted to alcohol while the majority does not.

2.3 Postoperative complications related to alcohol consumption and smoking

Both daily smokers and risky drinkers are overrepresented in hospital populations; depending on diagnosis and type of surgery up to five out of ten patients in elective surgery departments are risky drinkers [79] and smoking is associated with increased risk of hospitalization [80, 81]. Among middle-aged people 47 % of those who frequently drink more than 20 units of alcohol weekly are also daily smokers [82]. The threshold for an increased risk of complications may be as low as > 2 drinks per day [83] and because these patients often are relatively healthy staff may not be alerted to their hazardous alcohol intake at admission to surgery [84].
Daily smokers and risky drinkers are at increased risk of developing wound complications, general infections and pulmonary complications [1, 2] (Table 2). High alcohol consumption and daily smoking reduce the immune capacity leading to an increased risk of infection and impaired wound healing [79, 85]. In addition risky drinking increases the endocrine stress response to surgery, leading to deterioration of existing conditions which thus increases the risk of postoperative morbidity [1].

<table>
<thead>
<tr>
<th>Complications</th>
<th>RR</th>
<th>(95 % CI)</th>
<th>Complications</th>
<th>RR</th>
<th>(95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General morbidity</td>
<td>1.52</td>
<td>1.33-1.74</td>
<td>General morbidity</td>
<td>1.56</td>
<td>1.31-1.87</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1.73</td>
<td>1.35-2.23</td>
<td>Pulmonary</td>
<td>1.80</td>
<td>1.30-2.49</td>
</tr>
<tr>
<td>Wound complications</td>
<td>2.15</td>
<td>1.84-2.49</td>
<td>Wound complications</td>
<td>1.23</td>
<td>1.09-1.40</td>
</tr>
<tr>
<td>Admission to intensive care unit</td>
<td>1.60</td>
<td>1.14-2.25</td>
<td>Admission to intensive care unit</td>
<td>1.29</td>
<td>1.03-1.61</td>
</tr>
<tr>
<td>General infections</td>
<td>1.54</td>
<td>1.33-1.74</td>
<td>General infections</td>
<td>1.73</td>
<td>1.32-2.28</td>
</tr>
<tr>
<td>Neurological</td>
<td>1.38</td>
<td>1.01-1.88</td>
<td>Prolonged stay in hospital</td>
<td>1.24</td>
<td>1.18-1.31</td>
</tr>
</tbody>
</table>

2.4 Interventions for smoking and alcohol cessation
Numerous Cochrane reviews have evaluated different smoking cessation interventions: motivational interviewing [86], individual behavioural counselling [87], nursing interventions [88], physicians advice [89], interventions for hospitalized patients [90] combined pharmacotherapy and behavioural interventions for smoking cessation [91] and preoperative smoking cessation interventions [3] (Table 3).
Table 3: Effect of different interventions on smoking cessation

<table>
<thead>
<tr>
<th>Cochrane Review</th>
<th>Number of participants</th>
<th>Quality of the evidence (GRADE)</th>
<th>Follow-up</th>
<th>RR 95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motivational interviewing for smoking cessation [86] Compared to brief advice/usual care</td>
<td>16.803 (28 RCTs)</td>
<td>Moderate</td>
<td>≤6 months</td>
<td>RR 1.26 1.16 to 1.36</td>
</tr>
<tr>
<td>Individual behavioural counselling for smoking cessation [87] compared to usual care, brief advice or self-help materials. No systematic pharmacotherapy</td>
<td>11.100 (27 RCTs)</td>
<td>High</td>
<td>≤6 months</td>
<td>RR 1.57 1.40 to 1.77</td>
</tr>
<tr>
<td>Individual behavioural counselling for smoking cessation [87] compared to usual care, brief advice or self-help materials. Pharmacotherapy offered to all participants.</td>
<td>2.662 (6 RCTs)</td>
<td>Moderate</td>
<td>≤6 months</td>
<td>RR 1.24 1.01 to 1.51</td>
</tr>
<tr>
<td>Nursing interventions for smoking cessation [88]. High intensity intervention</td>
<td>13.613 (28 RCTs)</td>
<td>Moderate</td>
<td>≤6 months</td>
<td>RR 1.26 1.17 to 1.36</td>
</tr>
<tr>
<td>Nursing interventions for smoking cessation [88]. Low intensity intervention</td>
<td>4.016 (7 RCTs)</td>
<td>Moderate</td>
<td>≤6 months</td>
<td>RR 1.27 0.99 to 1.62</td>
</tr>
<tr>
<td>Physician advice for smoking cessation [89]. Minimal intervention</td>
<td>13.724 (17 RCTs)</td>
<td>Not reported</td>
<td>≤6 months</td>
<td>RR 1.66 1.42 to 1.94</td>
</tr>
<tr>
<td>Physician advice for smoking cessation [89]. Intensive intervention</td>
<td>8.515 (11 RCTs)</td>
<td>Not reported</td>
<td>≤6 months</td>
<td>RR 1.86 1.60 to 2.15</td>
</tr>
<tr>
<td>Interventions for smoking cessation in hospitalized patients [90]. Any hospital contact plus follow-up &gt; 1 month</td>
<td>7.403 (25 RCTs - quasi RCTs)</td>
<td>Not reported</td>
<td>≤6 months</td>
<td>RR 1.37 1.27 to 1.48</td>
</tr>
<tr>
<td>Interventions for smoking cessation in hospitalized patients [90]. Any hospital contact plus follow-up ≤ 1 month</td>
<td>4.476 (6 RCTs - quasi RCTs)</td>
<td>Not reported</td>
<td>≤6 months</td>
<td>RR 1.07 0.93 to 1.24</td>
</tr>
<tr>
<td>Combined pharmacotherapy and behavioural interventions for smoking cessation [91] compared to brief advice or usual care</td>
<td>19.488 (52 RCTs - quasi RCTs)</td>
<td>High</td>
<td>≤6 months</td>
<td>RR 1.83 1.68 to 1.98</td>
</tr>
<tr>
<td>Interventions for preoperative smoking cessation [3]. Brief intervention</td>
<td>1.141 (7 RCTs)</td>
<td>High</td>
<td>0-4 weeks</td>
<td>RR 1.3 1.16 to 1.46</td>
</tr>
<tr>
<td>Interventions for preoperative smoking cessation [3]. Intensive intervention initiated at least 4 weeks before surgery</td>
<td>210 (2 RCTs)</td>
<td>Moderate</td>
<td>0-4 weeks</td>
<td>RR 10.76 4.55 to 25.46</td>
</tr>
<tr>
<td>Interventions for preoperative smoking cessation [3]. Brief intervention</td>
<td>341 (2 RCTs)</td>
<td>Moderate</td>
<td>12 months</td>
<td>1.09 0.68 to 1.75</td>
</tr>
<tr>
<td>Interventions for preoperative smoking cessation [3]. Intensive intervention</td>
<td>209 (2 RCTs)</td>
<td>Moderate</td>
<td>12 months</td>
<td>RR 2.96 1.57 to 5.55</td>
</tr>
</tbody>
</table>

Motivational interviewing may assist people to quit smoking when compared to brief advice or usual care, but only when provided by trained counsellors [86]. Individual behavioural interventions increase the chance of quitting by between 40 % and 60 %, compared to minimal support. This effect decreased when all participants were offered Nicotine Replacement Therapy (NRT) support [87]. Brief, simple advice from doctors can increase the quit rate from 1-3 % to 2-6 %. Direct comparison of intensive
versus minimal advice suggested a small advantage of intensive advice and also a small benefit of follow-up visits [89]. Interventions provided by nurses have a potential benefit on smoking cessation. The evidence for an effect is weaker when interventions are brief and are provided by nurses whose main role is not health promotion or smoking cessation [88]. Interventions in hospitalized patients support smoking cessation only if the intervention is followed up after a minimum of four weeks [90]. Combined pharmacotherapy and behavioural interventions were also more effective than brief advice or usual care. From indirect comparison this review also found that interventions with 4-8 counselling sessions were not associated with larger treatment effects than 1-3 sessions [91].

The same pattern is found in preoperative smoking cessation interventions; both intensive and brief interventions initiated at least four weeks before surgery enhanced smoking cessation at the time of surgery, but after 12 months only intensive interventions had any effect [3].

Only two reviews have evaluated interventions in relation to alcohol abusers in hospital: brief interventions for heavy alcohol users admitted to general hospital wards [92] and preoperative interventions [4] (Table 4). The first review indicates that for general hospitals, there are benefits to delivering brief interventions to heavy alcohol users. At 6 months follow-up mean difference (MD) consumption of alcohol (grams per week) was -69.43, equalling 5-6 units [92]. A significant difference was not found three months postoperatively when the intervention was delivered to elective surgical patients preoperatively [4].

**Table 4**: Effect of interventions on alcohol cessation in different hospital settings

<table>
<thead>
<tr>
<th>Cochrane Review</th>
<th>Number of participants</th>
<th>Quality of the evidence (GRADE)</th>
<th>Follow-up</th>
<th>MD or OR 95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief interventions for heavy alcohol users admitted to general hospital wards [92]</td>
<td>4.041 (14 RCTs - CCTs)</td>
<td>Not reported</td>
<td>&lt;6 months</td>
<td>MD -69.43 -128.14 to -10.72</td>
</tr>
<tr>
<td>Preoperative alcohol cessation prior to elective surgery [4]</td>
<td>69 (2 RCTs)</td>
<td>Moderate</td>
<td>3 months</td>
<td>OR 18.47 0.93 to 368</td>
</tr>
</tbody>
</table>

1. Grams per week
Nicotine replacement therapy is a well-documented and safe drug used in smoking cessation interventions. The best effect is seen when a combination of different NRT products are used [71]. Other smoking cessation drugs are bupropion and varenicline. Bupropion seems to be less effective than varenicline [93], but all three products help people quitting smoking with low risk of harm [71]. NRT is sold over the counter, while bupropion and varenicline are obtained on prescription.

An overview and network meta-analysis of pharmacological interventions (NRT, bupropion, varenicline and cytisine) has been shown to improve the chances of quitting smoking, too. NRT products used in combination are as effective as is varenicline (RR 1.06; 95 % CI 0.75-1.48), but the latter is more effective than one NRT product used alone. Further research in the safety of varenicline is still warranted [71].

Disulfiram is a commonly used drug to treat people with alcohol use disorder and its supervised application has been shown to have some effect on short-term abstinence [94]. The effect is mainly thought to be psychological, because of the very unpleasant disulfiram-ethanol reaction caused by alcohol drinking and disulfiram treatment [95]. A systematic review shows that disulfiram is a safe and efficacious treatment, but only in single blinded RCTs. In double blinded RCTs there is no difference between treatment and control groups, indicating that it is the psychological threat of an aversive reaction and not the actual pharmacodynamic properties of the drug that works [96].

Few RCTs have evaluated the effect of smoking or alcohol cessation interventions on postoperative complications [79, 97-105], three of the studies enrolled cancer patients [97, 102, 103]. Interventions can roughly be divided into brief interventions and intensive ones. A brief intervention is a brief counselling session (face to face, via computer or letter) with or without pharmacotherapy, or pharmacotherapy with no counselling, while an intensive intervention includes weekly, individual behavioural counselling for 4–8 weeks with professionally trained smoking cessation counsellors with or without NRT [106]. There is evidence that brief smoking interventions do not reduce postoperative complications (RR 0.92; 95 % CI 0.72-1.19, while intensive interventions do reduce them ( RR 0.42; 95 % CI 0.27-0.65) [3]. Regarding alcohol there is evidence that intensive alcohol cessation interventions
reduce postoperative complications (follow-up four weeks) OR 0.22 (95% CI 0.08-0.61). No studies have evaluated the effect of brief alcohol cessation interventions on postoperative complications.

2.5 Surgery patients’ perspectives of smoking and alcohol interventions
Few studies have explored patient perspectives regarding smoking and alcohol cessation interventions in the perioperative period. Five qualitative studies, using semi-structured interview guides [107-111], combined the perspective of successful quitting and the perspective of successful outcome. They all found that participants were satisfied by being offered support in hospital to quit smoking or drinking prior to surgery and that the majority were motivated by the possible health gain following surgery. Naturally occurring health events like a cancer diagnosis have also been described as “a window of opportunity” to change lifestyle [112-115]; patients with cancer diagnosis are more likely to quit smoking than patients not so diagnosed [116-118]. It is well-known that cancer survivors are interested in lifestyle-interventions [119], but little is known about how cancer patients experience these interventions in the perioperative period [108, 120].

In summary, what is well-known today is that tobacco smoking is the most modifiable risk factor for developing UBC and that continued smoking after RC is associated with increased risk of progression, readmissions and cancer related death. Postoperative morbidity after RC remains high despite perioperative improvement. Tobacco smoking and risky alcohol drinking increase the risk of postoperative complications. The type of intervention that works best in smoking cessation is intensive interventions provided by trained counsellors and including combination NRT. In hospital settings the intervention must have at least four weeks follow-up after discharge. Regarding alcohol interventions more studies are needed to decide if intensive interventions work better than brief ones. Smoking and alcohol cessation interventions 4-8 weeks before surgery reduce the risk of postoperative complications, while preoperative brief interventions do not reduce their risk. Due to cancer pathway in Denmark preoperative interventions lasting 4-8 weeks are impossible today. The exact timing of a perioperative intervention to reduce the risk of postoperative complications is still unknown.
3. Hypotheses

Paper I
We hypothesized that patients undergoing robot assisted radical cystectomy had fewer postoperative complications than those undergoing open radical cystectomy within 30 and 90 days and had improved health related quality of life.

Paper II
We hypothesized that an intensive smoking and alcohol cessation intervention initiated at the earliest possible time before radical cystectomy, and continued 5 weeks after surgery, would reduce the postoperative complication rate from 50 % to 25 %.

Paper III
We hypothesized that an intensive smoking cessation intervention initiated at the earliest possible time before radical cystectomy, and continued 5 weeks after surgery would improve the cessation rate in the intervention group resulting in 50% of the patients in the intervention group stopping smoking in the perioperative period compared to 5 % in the control group.

Paper IV
In this paper we explored how bladder cancer patients experienced a perioperative smoking and alcohol cessation intervention in relation to radical cystectomy.
4. Aims

On the basis of the above described background, the objectives of the thesis are:

**Paper I**

1) To assess the number and types of postoperative complications within 30 and 90 days in patients undergoing RARC compared to ORC.
2) To assess the HRQoL in patients undergoing RARC compared to ORC.

**Paper II**

To describe the protocol for a six week intensive smoking and alcohol cessation intervention in relation to radical cystectomy on postoperative complications needing treatment.

**Paper III**

To evaluate the effect of a six week intensive smoking cessation intervention on quit rates after i) six weeks and ii) three months.

**Paper IV**

To explore how bladder cancer patients experienced a perioperative smoking and alcohol cessation intervention in relation to radical cystectomy and what facilitated smoking cessation.
5. Material and Methods

This thesis is based on two studies, a systematic review and meta-analysis, and the STOP-OP study. The trial profile and the publications in relation to the studies are illustrated in figure 2.

**Figure 2**: Trial profile for the STOP-OP study.
5.1 Study I

5.1.2 Paper I

Before starting the literature search for the review, a protocol was drawn up in compliance with the ‘Preferred Reporting Items for Systematic Reviews and Meta-Analyses’ (PRISMA) Statement [121] and was registered with the PROSPERO database in April 2016 (ID: CRD42016038232). A systematic review of the trials in the databases PubMed, Cochrane Library, Embase and CINAHL was conducted (Figure 3) to evaluate the evidence of robot-assisted radical cystectomy (RARC) versus open radical cystectomy (ORC) in regard to primary complications.

![Figure 3: PRISMA Flow chart literature search](image-url)
**Criteria for included studies**

RCTs comparing RARC to ORC and reporting at least one outcome of interest were included. The reconstruction method for urinary diversion should be described as extra-corporeal or intra-corporeal.

**Outcome measures**

In study I the primarily outcome was the number of patients with postoperative complications requiring treatment within 30 and 90 days. Secondary outcomes were grade 3-5 complications as defined by Clavien- Dindo [53], types of complications, length of stay (LOS), time back to work or habitual activity, and HRQoL.

**Data extraction and analysis**

After duplicates were removed the hits were transferred to Covidence [122]. Title and abstract screening was done by two of the authors. Data extraction was done individually by the same two people; any discrepancies were resolved by a third person. The quality of reporting of complications was assessed using the data extraction form from the EAU [55], (Table 5). To assess the risk of bias the Cochrane Collaboration tool was used [123]. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [124] to assess the quality of the evidence.
Table 5: Data extraction form for reporting of complications in surgical patients from EAU

| Study title:                      | ________________ |
| Published in:                    | __ European Urology |
|                                  | __ Journal of Urology |
|                                  | __ BJU International |
|                                  | __ Urology |
|                                  | __ World Journal of Urology |
| Year of publication:             | __ 1999-2000 |
|                                  | __ 2009-2010 |
| Volume:                          | ________________ |
| Page:                            | _____ to _____ |
| The study is a:                  | __ Case series |
|                                  | __ Controlled study without randomisation |
|                                  | __ Prospective randomised trial |
|                                  | __ Meta-analysis |
| Level of evidence (Oxford criteria, European Association of Urology modification): | __ 1a |
|                                  | __ 1b |
|                                  | __ 2a |
|                                  | __ 2b |
|                                  | __ 3 |
| The study reports complications after (define the procedure): | ________________ |
| Did the authors use standardized criteria: | __ Yes |
|                                  | __ No |
| In case standardized criteria were used, they were: | __ Predefined by authors |
|                                  | __ Clavien-Dindo system |
| No. Of Martin criteria met:      | __ 0-2 |
|                                  | __ 3-4 |
|                                  | __ 5-6 |
|                                  | __ 7-8 |
|                                  | __ 9-10 |

Review Manager (RevMan) was used for data analyses. To describe the observed intervention effect Mantel-Haenszel method was used to calculate RR with 95 % CI for dichotomous outcomes and inverse variance was used to calculate the mean difference and 95 % CI in the continuous outcome. A fixed-effect analysis was chosen, because it is assumed to be the best estimate of the intervention effect and heterogeneity was expected to be low [123]. Heterogeneity was calculated using $I^2$ statistics, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. If heterogeneity among studies exceeds 60 %, reasons for heterogeneity were further explored [123]. Sub-group analyses according to types of complications were also made.
5.2 Study II

Data presented in paper II, III and IV are from patients joining the prospective RCT STOP smoking and alcohol drinking before OPeration for bladder cancer (the STOP-OP study), perioperative smoking and alcohol cessation intervention in relation to radical cystectomy. Paper II [125] describes the protocol for the trial, paper III reports the results from the first 50 consecutive patients enrolled in the STOP-OP study and paper IV is a qualitative study exploring how participants in the intervention group experienced the smoking and alcohol cessation intervention.

The STOP-OP study is currently being conducted at the Departments of Urology at Aalborg University Hospital, Aarhus University Hospital Skejby, Copenhagen University Hospital Herlev and Copenhagen University Hospital Rigshospitalet. The study was registered in the Clinical Trials.gov database on 28 May 2014 (ID: NCT02188446). The trial was approved by the Danish Scientific Ethical Committee System (H-1-2013-134) [126], as well as the Danish Data Protection Agency (2012-58-0004). All patients signed informed consent before randomization. The trial was reported in concordance with the CONSORT statement [127]

5.2.1 Paper II

Participants

All patients who were daily smokers and/or drinking >20 units of alcohol per day and scheduled for RC because of UBC were assessed for eligibility at the participating urological departments. Exclusion criteria were: patients with known allergies to NRT or disulfiram, pregnant or breastfeeding women and patients with mental disorders not being able to sign informed consent.

Outcome measures

The primary outcome was the number of patients who developed any postoperative complication, or death, within 30 days after surgery. Secondary outcomes were: types and grades of complications within 30 and 90 days after surgery according to the Clavien-Dindo classification [53]. Postoperative complications were evaluated prospectively by patient interview at follow-up meetings after 6 weeks, 3, 6 and 12 months and retrospectively by a urologist blinded to the patients’ group allocation.
**Sample size and statistics**

Based on previous studies reduction of postoperative complications after intensive smoking and alcohol cessation interventions [4, 98-100], our aim was to reject or confirm a reduction from 50 % to 25 % in the number of patients who develop any postoperative complication. With a type 1 error risk of 5 %, and a type 2 error risk of 20 % (80 % power), the required sample size is 55 patients in each group.

All analyses will be conducted by an independent researcher using intention-to-treat principles. If data are not normally distributed, non-parametric tests are performed. Continuous variables are presented as median and range; categorical variables are presented as counts. The effect of the intervention on risk of postoperative complications and smoking/alcohol abstinence is analyzed by Fisher’s exact test. Test of the effect of the intervention for LOS and HRQoL scores is analyzed by Mann-Whitney’s test. If $p$-values are less than 0.05, effects are considered statistically significant.

**Standard care**

Patients in the control group received information about the background, objectives and potential implications of the current trial and they were provided with Danish information packs on alcohol and tobacco and surgery. This entails written information about the risks of smoking and drinking in relation to surgery according to national guidelines. Patients were encouraged to follow these guidelines and assured that they were free to access smoking-cessation and/or alcohol-cessation support services in the hospital or elsewhere if they wished.

**Intervention**

Patients in the intervention group received five counselling sessions before and after surgery over 6 weeks with trained smoking and alcohol cessation counselors in accordance with the Gold Standard Programme [128] (Table 6). The principles of motivational interviewing and the trans-theoretical model of change are the underlying tenets of the programme. Key to the intervention is a patient-centered approach that encourages patients to consider pros and cons of behavioural change and their motivation for change. The counselor’s primary role is to ask, listen and follow the patient’s cue and to adapt formal information to the patient’s motivational stage. Three tools help the counselors do this: the LINE, the BOX and the CIRCLE. The LINE is an easy to use visual analogue scale (VAS) from 0-10 on which patients score: (1) the importance of stopping smoking and/or drinking in relation to their
surgery; and (2) their self-confidence in being successful in stopping. The BOX consists of four open squares where patients are asked to write their thoughts about advantages and disadvantages of stopping and not stopping. Together, the LINE and the BOX facilitate contemplation of change in patients and establish a common ground for supporting change. The CIRCLE is a model representation of the stages people go through during the process of change. It primarily helps the counselor to choose how best to support the patient (See paper II). The LINE, BOX and CIRCLE are incorporated into each counseling session. At the first session, patients are encouraged to stop smoking and drinking alcohol at the latest 1 day before surgery, preferably earlier, and to abstain for 5 weeks after surgery. Smokers are encouraged to quit smoking entirely. In the 6-week intervention period, smokers are offered a personalized NRT schedule devised in accordance with patient preferences and nicotine dependency assessed by the Fagerström’s Test [129] for nicotine dependency. Risky drinkers are offered supportive medicine against development of mild to moderate withdrawal symptoms (chlordiazepoxide 10 mg).

Table 6: The Gold Standard Programme for smoking and alcohol cessation

<table>
<thead>
<tr>
<th>Patient education programme</th>
</tr>
</thead>
<tbody>
<tr>
<td>First meeting (before admission)</td>
</tr>
<tr>
<td>o Level of motivation, ambivalence, pros and cons</td>
</tr>
<tr>
<td>Second meeting (after 1 week)</td>
</tr>
<tr>
<td>o Dependence, withdrawal symptoms (experience and expectations)</td>
</tr>
<tr>
<td>Third meeting (after 2 weeks)</td>
</tr>
<tr>
<td>o Relapse (description and management)</td>
</tr>
<tr>
<td>Fourth meeting (after 3 weeks)</td>
</tr>
<tr>
<td>o Benefits of short and long term smoking and/or alcohol abstinence</td>
</tr>
<tr>
<td>Fifth meeting (after 5 weeks)</td>
</tr>
<tr>
<td>o Continued smoking abstinence and/or reduced alcohol intake following intervention</td>
</tr>
</tbody>
</table>

At each meeting

Smokers: Personalized Nicotine Replacement Therapy (NRT) in accordance with patient preferences and nicotine dependency
Risky drinkers: Thiamine and B-vitamins (300 mg daily)
Alcohol withdrawal prophylaxis and treatment (chlordiazepoxide 10 mg as required)
Disulfiram (200 mg x 2 weekly) supervised at weekly meetings (not administrated if patients test positive on breath test)
All: Hemoglobin, liver enzymes and alcohol biomarkers (blood, urine), CO and alcohol breath test, lung function test

The study medication is provided for free and transportation for the weekly meetings will be reimbursed. Patients have telephone access to the research nurse.
5.2.2 Paper III

Participants

Identical with paper II

Outcome measures

The outcome measure was the 7-day abstinence rate at six weeks and continuous abstinence rate at three months after the initial quit date. Abstinence was self-reported and verified biochemically. Participants in the intervention group underwent a breath test at each visit and participants in the control group at inclusion and at each follow-up. All trial sites used U-blow CO-monitor Model 381150 to measure CO in exhaled air. In accordance with the literature CO cut-off for smoking abstinence was set at 4 ppm [130, 131].

Sample size and statistics

The sample size was based on the expected effect of the clinical outcome smoking cessation. Based on previous studies using intensive interventions [98, 99] we assumed that 50 % of the patients in the intervention group would stop smoking in the perioperative period compared to 5 % in the control group. With a type 1 error risk of 5 %, and a type 2 error risk of 10 % (90 % power), the required sample size was 19 patients in each group. To respond to a potential drop-out rate of 20 % it was decided to include 50 patients.

Demographic data were presented with descriptive statistics. Continuous variables were presented as medians and ranges, while categorical variables were presented as counts and ranges. We used logistic regression models to do the statistical analysis of the association between intervention and probability of smoking abstinence at 6 weeks and 3 months. Estimates of the difference between treatment groups were reported as Odds Ratio (OR) with 95 % confidence intervals. We considered $p$-values $\leq 0.05$ statistically significant. We fitted both unadjusted models defining the intervention group as independent variable and adjusted models including age and sex. Using an unadjusted logistic regression model we made a subgroup analysis for all patients comparing self-reported smoking abstinence to the CO validation. The analysis followed the Intention-To-Treat (ITT) approach [132],
where group comparisons were based on the initial group assignment, regardless of intervention completion. All analyses were done by an independent researcher using R 3.2.2 [133].

**Intervention and standard care**

Identical with paper II

5.3 Paper IV

Paper IV is based on study II. We performed a qualitative study to gain knowledge about how bladder cancer patients experienced the perioperative smoking and alcohol cessation intervention in the STOP-OP study. The protocol for this study was written in compliance with the COREQ guidelines [134]. The Danish Scientific Ethical Committee System (16040244) evaluated the study protocol and found formal appraisal of the study to be unnecessary. The Danish Data Protection Agency (2012-58-0004) approved the study. All patients received both oral and written information and signed informed consent before being interviewed.

**Design**

The study was based on a qualitative descriptive design to obtain in-depth knowledge about how newly diagnosed cancer patients experienced the intensive smoking and alcohol cessation interventions in relation to major bladder surgery. Inspired by a phenomenological – hermeneutical method [135] we conducted semi-structured in-depth interviews.

**Participants and setting**

Fourteen patients were invited to participate in the qualitative study between November 2016 and May 2017. Three patients declined participation and gave the reason that they did not want to be interviewed. All participants were recruited from the STOP-OP intervention group after completion of the 6-weeks intervention. The interviews lasted 20-40 minutes and were all conducted in the urological departments in which the patient had a scheduled out-patient visit.
**Data collection and analysis**

The strategy for including participants in the study was to use the principle of purposeful sampling with maximum variation [136] to achieve a varied sample with respect to: age, smoking and/or alcohol consumption and success or failure in abstaining. Data were collected until saturation [137]. A semi-structured interview guide with open-ended questions was prepared beforehand to ensure coverage of the research questions (see paper IV). The interviewer asked broad questions to explore the individual’s experience.

The interviews were digitally recorded and transcribed verbatim. The software program QSR NVivo (version 11) was used for data managing. The analysis model is adapted based on some of the principles of argumentation theory as described by Toulmin (Figure 4). Our analysis followed the steps contained in the thematic network analysis [138]. The process can be split into three broad stages: (1) the reduction or breakdown of the text (2) the exploration of the text; and (3) the integration of the exploration [138]. In the analysis process the network was continuously explored by consulting the interview text until the findings were interpreted.

*Figure 4: Structure of a thematic network*

![Diagram of a thematic network](image)

*Figure 4 shows the similarities between the formal elements of an argument as described by Toulmin: the progression from accepted data (quotes from participants not included in this model) through a warrant (basic themes) and to a claim (global theme). The organizing themes group the main ideas from several basic themes and are the principles on which a superordinate claim is based.*
6. Results

6.1 Paper I
The literature search yielded a total of 273 records. Of these, 261 were excluded as they had no relevance to this review. This left 12 potentially relevant studies, of which five articles, covering four studies, fulfilled the inclusion criteria [139-143].

Characteristics of included studies
The four RCTs included had a total of 239 patient cases, ranging from 40 to 118 patients in each trial. 118 patients underwent ORC and 121 underwent RARC. Approximately 80 % of the patients were male. One study did not describe the type of urinary diversion performed; the remaining ones performed extra-corporeal urinary diversion. ASA scores were comparable across studies with the majority of the patients having an ASA score of 2-3.

Reporting of complications
The reporting of complications was generally poor. Three studies classified complications according to the “Clavien-Dindo” classification [53] and one study [144] used the Memorial Sloan Kettering Cancer Center (MSKCC) modified “Clavien-Dindo” classification [47]. This should make comparison feasible, but in one study [139] it was unclear if all grades had been assessed, in two studies only grade 2-5 complications were reported [140, 142] and none of the studies included blood transfusion as a complication even though this is a grade 2 complication according to the Clavien-Dindo classification system [54]. Three studies [139, 140, 142] met five of the ten Martin et al. criteria [55, 145] and one study [143] met eight of the ten criteria.

Quality assessment
Overall, the studies were assessed to be at moderate risk of bias (Figure 5) and the quality of the evidence was considered to be low for complications and moderate for LOS (Table 7).

![Figure 5: Summary of quality assessment of risk of bias](image)

We judged blinding of participants and personnel as low risk of bias because we considered it unlikely to influence the primary outcome.
### Table 7: Quality assessment of the evidence across studies; summary of findings

<table>
<thead>
<tr>
<th>Activity</th>
<th>work or physical activity</th>
<th>Time back to work or habitual</th>
<th>Number of patients with complications within 90 days</th>
<th>Time to 1st intervention (days)</th>
<th>Number of patients with complications within 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW (4/7)</td>
<td>0 (0/0)</td>
<td>0 (0/0)</td>
<td>0 (0/0)</td>
<td>0 (0/0)</td>
<td>0 (0/0)</td>
</tr>
<tr>
<td>MODERATE (3/7)</td>
<td>1.8 (1.6/2.0)</td>
<td>5 (5/5)</td>
<td>2 (2/2)</td>
<td>292 (292/292)</td>
<td>512 (512/512)</td>
</tr>
<tr>
<td>HIGH (2/7)</td>
<td>1.4 (1.0/2.0)</td>
<td>9 (9/9)</td>
<td>5 (5/5)</td>
<td>792 (792/792)</td>
<td>1172 (1172/1172)</td>
</tr>
<tr>
<td>VERY HIGH (1/7)</td>
<td>0 (0/0)</td>
<td>13 (13/13)</td>
<td>10 (10/10)</td>
<td>379 (379/379)</td>
<td>679 (679/679)</td>
</tr>
</tbody>
</table>

**Note**: The table above presents a summary of findings for the quality assessment of evidence across studies. The data includes the activity, time back to work or habitual, number of patients with complications within 90 days, time to 1st intervention (days), and number of patients with complications within 30 days. The findings are categorized into four levels: LOW, MODERATE, HIGH, and VERY HIGH, each with a corresponding score and range of values.
Meta-analyses

Five meta-analyses were conducted comparing RARC and ORC and the outcomes were 1) Number of patients with complications within 30 days, 2) Number of patients with complications within 90 days, 3) Number of grade 3-5 complications within 30 days (Total complications grade 2-5), 4) Number of grade 3-5 complications within 90 days (Total complications grade 2-5) and 5) Length of stay.

The pooled effect sizes showed no statistically significant difference between RARC and ORC in the number of patients developing complications within 30 days postoperatively: RR 0.78 (95 % CI, 0.53-1.16; p= 0.22) or 90 days postoperatively: RR 0.90 (95 % CI, 0.71-1.14; p= 0.39). Regarding overall grade 3-5 complications within 30 days postoperatively: RR 1.07 (95 % CI, 0.61-1.87; p= 0.82) and 90 days postoperatively: RR 1.04 (95 % CI, 0.64-1.71; p=0.87). There was no heterogeneity ($I^2 = 0 \%$) in any of the meta-analyses.

6.2 Paper II

At this stage of reporting, 86 patients have been enrolled in the study; 62 to the smoking cessation intervention, 12 to the alcohol intervention and 12 to the combined smoking and alcohol intervention. Patient accrual is expected to be finalized between the end of 2017 and early 2018 and 12 months follow-up results from the trial will be published in early 2019.

6.3 Paper III

Patient characteristics

To enroll 50 patients, a total of 629 patients were screened from November 2014 to February 2017. 473 patients did not meet the inclusion criteria, 86 declined participation and 20 patients were not asked to participate in the study (Figure 6). After randomization three patients in the intervention group had surgery cancelled and were excluded from analysis. At baseline patients were comparable in the intervention and control group (Table 8), except for neoadjuvant chemotherapy.
Figure 6: Flowchart of the recruitment according to the Consort Statement

- **629 patients screened**
- **579 excluded**
  - 473 not meeting inclusion criteria
  - 86 declined to participate
  - 20 not asked
- **50 Randomised**
- **26 allocated to intervention**
  - 23 received intervention
  - 3 had no RC
- **24 allocated to control**
  - 24 received standard care

Follow-up 6 weeks
- 0 lost to follow-up

Follow-up 3 months
- 1 lost to follow-up (dead)

Analysis
- 23 (22) analysed

0 lost to follow-up
- 24 analysed
Table 8 Patient characteristics in 47 patients from the STOP-OP study

<table>
<thead>
<tr>
<th></th>
<th>Intervention n = 23</th>
<th>Standard n = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>21 (91)</td>
<td>15 (63)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>2 (9)</td>
<td>9 (37)</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>67 (43-77)</td>
<td>68 (48-78)</td>
</tr>
<tr>
<td>BMI median (range)</td>
<td>25 (18-33)</td>
<td>25 (15-41)</td>
</tr>
<tr>
<td>Fagerströms score, median (range)</td>
<td>4.0 (0-6)</td>
<td>4.0 (0-8)</td>
</tr>
<tr>
<td>CO, median (range)</td>
<td>7.0 (0-49)</td>
<td>7.5 (0-28)</td>
</tr>
<tr>
<td>Age at start of smoking, median (range)</td>
<td>15 (10-30)</td>
<td>15.5 (8-22)</td>
</tr>
<tr>
<td>Pack-years, median (range)</td>
<td>43 (9-96)</td>
<td>46 (17-83)</td>
</tr>
<tr>
<td>Living with a smoker, n (%)</td>
<td>13 (28)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Previous quit attempts, median (range)</td>
<td>2 (0-10)</td>
<td>1 (0-20)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index Score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2 (9)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>1-2 Low</td>
<td>4 (17)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>3-4 High</td>
<td>13 (57)</td>
<td>14 (58)</td>
</tr>
<tr>
<td>≥ Severe</td>
<td>4 (17)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Had neoadjuvant chemotherapy, n (%)</td>
<td>9 (31 %)</td>
<td>1 (3.4 %)</td>
</tr>
<tr>
<td>AUDIT-C, median (range)</td>
<td>3 (0-7)</td>
<td>4.5 (0-9)</td>
</tr>
</tbody>
</table>

Findings

Adherence to the intervention was very high; 91 % participated in all five meetings. The self-reported abstinence rate after the 6 week intervention was 57 % in the intervention group and 33 % in the control group (Table 9 and Figure 7). The difference between groups was less than previously anticipated. Unadjusted analysis showed non-significant change in odds of abstinence for the intervention group compared to the control group at 6 weeks follow-up OR = 2.6 (95 % CI: 0.8 – 8.5 p = 0.19) and at 3 months OR = 1.0 (95 % CI: 0.3–3.6, p = 1). Adjusting for sex and age increases the odds of abstinence for the intervention group to a significant level after the 6 week intervention, OR = 5 (95 % CI: 1.1–23.1, p = 0.04), but results at 3 months was still non-significant OR = 1.9 (95 % CI: 0.4-9.2. p = 0.43). Looking at the CO threshold of < 4 in the 21 patients that reported cessation, the result did not change: OR 2.5 (CI: 0.12 - 50.4, p = 0.55).
Table 9: Self-reported and biochemically validated smoking cessation after 6 weeks.

<table>
<thead>
<tr>
<th>Smoking cessation by</th>
<th>Intervention</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods of measurement</td>
<td>N = 23</td>
<td>N = 24</td>
</tr>
<tr>
<td>Self-report smoking</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Self-report no smoking</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>CO ≤ 4</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>CO &gt; 4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Not CO validated</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

1Patient in intensive care unit, 2 Telephone meeting

In the intervention group 15 people stopped smoking 1-2 day prior to surgery and 16 people (70 %) relapsed within 2 months of surgery (Figure 8).

Figure 8: Patterns of smoking relapses within 3 months in the intervention group

Note that intervals before operation are different than after operation to make clear how close to surgery the majority of the patients chose their stop date.
6.4 Paper IV

Participant characteristics

Eleven participants, 10 men and 1 woman, aged 43-77 were interviewed (Table 10).

Table 10: Characteristics of the 11 participants interviewed

<table>
<thead>
<tr>
<th>Participant characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, median (range)</td>
<td>58 (43-77)</td>
</tr>
<tr>
<td>Age at smoking debut, median (range)</td>
<td>15 (7-19)</td>
</tr>
<tr>
<td>Pack years, median (range)</td>
<td>43 (26-54)</td>
</tr>
<tr>
<td>Fagerströms Nicotine Dependency score, median (range)</td>
<td>4.5 (3-6)</td>
</tr>
</tbody>
</table>

Type of intervention

- Smoking cessation intervention (n) 6
- Alcohol cessation intervention (n) 3
- Smoking and alcohol cessation intervention (n) 2

Smoke and alcohol free during the 6-weeks intervention (n)

- Yes 8
- No 3

Smoke-free / alcohol reduction at the interview (n)

- Yes 5
- No 6

Living with a smoker (n)

- Yes 4
- No 7

Surgical procedures (n)

- Ileal conduit 8
- Neobladder 2
- Continent cutaneous diversion 1

Findings

Two global themes emerged to explain how the bladder cancer patients experienced the smoking and alcohol cessation intervention in relation to radical cystectomy: 1) Smoking and alcohol cessation was experienced as an integral part of bladder cancer surgery and 2) Returning to everyday life was a barrier for continued smoking cessation/alcohol reduction. The smoking and alcohol cessation interventions were well received by the participants. The participants in this study wanted support to stop smoking and risky drinking during hospitalization and did not feel the intervention as a burden, but as an integral part of preparation for surgery. The fact that they also felt a need for continued support when returning to everyday life points to the need to further explore if extended follow-up with educational support could maintain long-term smoking cessation and alcohol reduction (Figure 9).
**Figure 9**: Thematic network for “Smoking and alcohol cessation intervention is experienced as an integral part of radical cystectomy”
7. Discussion

The objectives of this thesis were to evaluate complications and smoking cessation in relation to radical cystectomy and to explore patients’ experience of the 6 week smoking and alcohol cessation intervention.

7.1 Complications

As the STOP-OP study is ongoing, we do not yet know whether the smoking and alcohol cessation intervention will reduce the postoperative complication rate in patients undergoing RC. The systematic review and meta-analyses showed that patients with bladder cancer undergoing RARC did not develop fewer complications or have reduced length of stay compared to patients undergoing ORC. More studies are needed on patient-related outcomes like HRQoL and time back to work. The key finding was that even though the Clavien-Dindo classification system was used in all studies on which we have drawn, the inconsistent reporting of complications and the quality of the evidence impeded firm conclusions. This finding will help us report the complications in the STOP-OP study in a meticulous way in accordance with the EAU guidelines [146] and thus make possible comparison with future studies.

The frequency of complications is high in RC, ranging from 11-93 % depending on the definition of a complication [20, 47, 147-149]. It is suggestive that in our systematic review the number of people with complications within 30 days ranged from 26 % to 63 % [46]. Two studies [140, 142] reported only grade 2–5 complications and it is unclear if all grades were assessed in Nix et al. [139] as they reported only median and mean values for the Clavien-Dindo units. Although it can be argued that grade 1 complications are unimportant from a clinical perspective, they may not be so from a patient perspective. A careful reporting of complications and other data as described by Martin et al. (see table 11) [145] is of importance to compare treatments and to make recommendations for clinical practice.
Table 11: Martin et al. criteria for reporting of surgical complications [146]

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Method of accruing data defined</td>
<td>Prospective or retrospective accrual of data are indicated</td>
</tr>
<tr>
<td>2) Duration of follow-up indicated</td>
<td>Report clarifies the time period of postoperative accrual of complications such as 30 d or same hospitalisation</td>
</tr>
<tr>
<td>3) Outpatient information included</td>
<td>Study indicates that complications first identified following discharge are included in the analysis</td>
</tr>
<tr>
<td>4) Definition of complications provided</td>
<td>Article defines at least one complication with specific inclusion criteria</td>
</tr>
<tr>
<td>5) Mortality rate and causes of death</td>
<td>The number of patients who died in the postoperative period of study are recorded together with causes of death</td>
</tr>
<tr>
<td>6) Morbidity rate and total complications indicated</td>
<td>The number of patients with any complication and the total number of complications are recorded</td>
</tr>
<tr>
<td>7) Procedure-specific complications included</td>
<td></td>
</tr>
<tr>
<td>8) Severity grade utilised</td>
<td>Any grading system designed to clarify severity of complications including major and minor are reported</td>
</tr>
<tr>
<td>9) Length-of-stay data</td>
<td>Median or mean length of stay indicated in the study</td>
</tr>
<tr>
<td>10) Risk factors included in the analysis</td>
<td>Evidence of risk stratification and method used indicated by study</td>
</tr>
</tbody>
</table>

Comparison with findings from other studies
We registered the protocol for the systematic review with the PROSPERO database in April 2016 and since then two other systematic reviews comparing RARC to ORC based on the same four RCTs were published [150, 151]. Even though Tan et al. [150] and Shen et al. [151] did not distinguish between complications within 30 and 90 days, but pooled data, they reached the same conclusion as we did regarding overall complications.

Quality of the evidence
The first reviews to compare RARC to ORC were based on both RCTs and observational studies [152-156] and they all concluded that patients undergoing RARC might benefit from significantly fewer total complications. The recent reviews including only RCTs [46, 150, 151] come to a different result. To know if an intervention is recommendable we must have confidence in the effect estimate [124] and this is why evaluation of the quality of the evidence is important. To our knowledge our systematic review is the first study comparing RARC to ORC to use the GRADE approach to evaluate the quality of the evidence. A recommendation to offer patients RARC should preferably arise from large, rigorous randomized controlled trials that show consistent benefits of RARC compared to ORC with few side effects and minimal inconvenience and cost. To date only small RCTs have been carried out and without
rating the quality of evidence of these studies there is a risk that the effect estimates leads to misguided recommendations regarding the benefits of robot-assisted surgery. As the results of our meta-analyses are based upon low to moderate quality of the evidence, we still do not know if RARC is superior to ORC regarding complications and LOS. The results from the RAZOR study [157] may help answer this question.

7.2 Smoking cessation

The RCT reported in paper III looked at one of the secondary outcomes in the STOP-OP study, i.e. smoking cessation. We showed that the GSP intervention was successful as 57% in the intervention group were abstinent after 6 weeks compared to 33% in the control group, although the difference in the unadjusted analysis was not significant OR 2.6 (95% CI: 0.8 – 8.5 p = 0.19). This indicates we might have a type-2 error and further data from the STOP-OP study might change this. After 3 months there were no difference at all between the groups, 30% were abstinent in both groups. Interestingly only one patient in the control group relapsed while more relapses were seen in the intervention group. This finding suggests that the intervention might support patients who are less likely to stay abstinent in the perioperative period. Even though the randomized design balances and adjusts for both measured and unmeasured confounders, it has been discussed whether or not results from regression adjustment are more meaningful from a clinical perspective because randomization may be insufficient to achieve balanced groups in studies with fewer than 200 patients [158, 159]. On this background we decided to present adjusted results, reducing the risk of confounding due to possible uneven distribution among the groups in our relatively small sample. Adjusting for sex and age we observed a statistically significant positive effect of the intervention for 6 weeks abstinence, p = 0.04 However looking at the wide confidence intervals (1.1-23.1), indicating that the estimate could be anywhere between a 10% to a 23 times larger odds, the exact beneficial effect is hard to specify. Therefore the result should be interpreted with caution.

Comparison with findings from other studies

More RCTs have evaluated a perioperative smoking cessation intervention [98-104, 118, 160] with inconsistent results; Six studies [98-100, 102, 160] found a significant difference in the abstinence rate from 14-60% in the intervention group compared to 2-20% in the control group (follow-up from 30 days to 6 months), while two studies [104, 118] found no difference; intervention group from 5 to 32% compared to an identical range in the control group. The study from Ostroff et al. and our study both had a high biochemically verified abstinence rate observed after 3 and 6 months respectively. This could be explained from the fact that the oldest studies intervened on general surgery patients and the latter on cancer surgery patients who might be more encouraged to stop smoking because of the cancer diagnosis [116, 117]. However, the study from Thomsen et al. [102] contradicts this explanation.
Shorter quit duration before surgery has been associated with greater risk of relapse [161, 162]. Cooley et al. found that 60% of smoking relapses occurred within 2 months postoperatively [162]. In our study 70% of the patients had relapsed within 2 months after surgery. This supports the finding from the qualitative study that feeling better and returning to everyday life after surgery increases the risk of relapse and indicates that longer interventions should be considered.

We found a high adherence to the intervention meetings and the adjusted analyses showed a five times larger odds for smoking abstinence after the intervention. Similar to our findings Neumann et al. showed an association between adherence to meetings and smoking cessation in heavy smokers; heavy smokers had 4.36 times higher success with smoking cessation when they attended at least 75% of the meetings [163]. Rasmussen et al. also found an association of compliance with meetings and abstinence rate after six months [164]. 77% of the participants in our study were men and, interestingly, Rasmussen et al. also found that short interventions were more effective in men. This might partly explain the high quit rate in the control group.

7.3 Patient perspectives

The qualitative study provided knowledge from the patient perspectives about the intervention in the STOP-OP study. The study participants had a positive response to the intervention. The main findings from the interviews were that bladder cancer patients did not see the smoking and alcohol intervention as a separate part of preparation for surgery, but as an integral part of it. This might partly explain why they also found returning to everyday life a barrier for continued smoking cessation and alcohol reduction, because surgery became past and everyday life present. Few studies have investigated the experiences of smoking and alcohol cessation interventions in relation to cancer surgery [108, 120]. Farley et al. explored the views of surgical lung cancer patients views about smoking cessation as a part of cancer care and found that participants found it easy to be abstinent in hospital but relapsed at home [120]. In the study from Thomsen et al. women with breast cancer were interviewed about their experience of a brief smoking cessation intervention in relation to surgery. They were recommended smoking cessation 10 days postoperatively [108]. Most study participants found smoking cessation easy, but some found attempting it to be difficult concurrent with coping with the anxiety of a breast cancer diagnosis [108]. In our study the participants found smoking cessation easy and did not see it as an extra burden during surgery. These findings support existing evidence that there might be advantages of integrating smoking cessation interventions more effectively into routine practice [120, 165] and that the reluctance from healthcare professionals to talk with cancer patients about smoking and alcohol cessation [166-168] is without foundation; cancer patients are interested in these interventions [107, 109]. Our study extends previously findings by interviewing patients recovering from curative surgery for bladder cancer.
7.4 Strengths and limitations

Study II has some limitations. Firstly there was performance bias because blinding of participants and personnel was not possible. It is not clear whether there was an unintended systematic difference in the delivering of the intervention happened. RCTs aim to produce minimally biased estimates of the intervention but have been criticized for not being the best design when evaluating complex interventions, because the effect can be diluted by ‘contamination’ effects in un-blinded interventions [169, 170]. By addressing intervention fidelity [171] we tried to reduce the risk of ‘contamination’ between groups. We had all counsellors participate in a three- day course in the GSP and everyone had a protocol for both intervention and control group that outlined the content of each meeting. There was regular contact with the counsellors from the study leader to discuss the intervention and potentially problems. However, we did not assess the participants understanding and performance of the intervention [171]. Despite these limitations, we still believe that the RCT design provided the strongest evidence about the effectiveness of this smoking cessation intervention. The use of a computer-generated stratified, block randomization scheme was a strength in this study and meant we had a very low risk of detection bias. This was also the case with attrition bias [123]. We also followed the Russell criteria [172] and measured abstinence both as self-reported and CO validated.

One limitation to the qualitative study is that the participants represent a somewhat motivated group, having voluntarily taken part in the STOP-OP trial. A strength of this study is that it helps us understand the social world and provides knowledge about how the participants experienced the smoking and alcohol cessation intervention. A common criticism of qualitative research is that it is superficial and describes common sense knowledge. We aimed at conducting and presenting our analysis as rigorously as possible, as recommended by Guba [173]. It can be argued that our findings represent the experiences of only eleven participants and that these findings cannot be transferred to other cancer patients, but as our findings are consistent with those from other qualitative studies [120, 165] we believe transferability is possible to other cancer patients resembling our study participants.
8. Conclusions

This thesis adds to the limited evidence on lifestyle interventions in patients undergoing RC. From the systematic review (study I) we found out that robot assisted surgical technique did not significantly reduce complications and LOS or improve HRQoL compared to ORC. In study II we evaluated smoking cessation in relation to RC. We found no evidence that a 6-week smoking cessation intervention significantly reduced smoking by 50% more than standard treatment did. However, the abstinence rate after 6 weeks was high in both the intervention and control group and adjusted analysis showed a beneficial effect of the intervention. This indicates that the timing of the intervention was the right moment to address smoking cessation. The qualitative study in study II explored the patient perspective and we found that patients from the intervention group received the smoking and alcohol cessation intervention well. Major bladder cancer surgery served as a kind of refuge and integrating the smoking and alcohol cessation intervention in preparation for surgery was seen as a good support to quit smoking and to reconsider the consequences of risky drinking. The risk of relapse increased with patients feeling better and returning to everyday life.

9. Future perspectives

9.1 Implication for research

Findings from study II, paper III and IV show that the timing of the intervention in relation to bladder cancer surgery is well-planned, but that the risk of relapse increased concurrently with increased feeling of well-being. These findings suggest that more research is needed to decide how long the cessation support should last in order to enhance long-term cessation. On the whole all patients in the control group remained abstinent at 3 months. This finding suggests that some people are able to quit with minimal support and the mechanism behind this result should be further explored. As more cancer patients survive today, there is a growing realisation that more research addressing interventions that will prevent or reduce adverse outcomes after cancer treatment is needed [174, 175]. Cancer prehabilitation is a way of doing this as it addresses assessment of the patient at the time of diagnosis to establish a baseline functional level, identifying impairments and provide relevant interventions to promote physical and psychological health [176]. However, interventions started during prehabilitation are not limited in use to the time before cancer treatments begin, use of these interventions may continue throughout survivorship [175].

The results from paper III showed that the abstinence rate in both intervention and control group was very high indicating that patients undergoing major bladder cancer surgery are interested in optimizing their physical condition to prevent postoperative complications. The primary outcome of the STOP-OP study is postoperative complications and as we still do not have data from the combined smoking and alcohol cessation intervention, we do not know if this intervention works. Smoking has a documented
association with numerous postoperative complications [175]. If our smoking and alcohol cessation intervention does not reduce postoperative complications, further research should look into a multimodal approach including nutritional optimization and physical exercise to find out if a combined intervention proves to be more effective.

9.2 Implications for practice

Step one in prehabilitation is to assess the cancer patient to identify risk factors that compromise surgery and step two to start interventions. In a comment to a Cochrane review about brief motivational interviewing in young adults with alcohol misuse Grant et al. question the way we interpret effect sizes and the difference between statistical significance and clinical significance [177]. Our study did not find a significant difference between the intervention and control groups, but the high abstinence rate in both groups supported by the adjusted analysis makes the difference clinical relevant and shows that an intensive intervention motivates more than 50 % to stop smoking in relation to bladder cancer surgery. It also showed that addressing smoking cessation and encouraging patients in the control group motivated 30 % to stop. This means that clinical practice can use different tools for smoking cessation interventions depending on local resources.

This prospective RCT provides for the first time evidence for a smoking cessation intervention in RC pathways with the possibility of improving clinical outcomes.

9.3 Implications for patients

The results from paper I, III and IV are important to future patients undergoing RC, because they point to the safety of RC independent of surgical technique and to the feasibility of integrating smoking and alcohol cessation interventions in RC pathways. The greatest barrier for implementing these lifestyle interventions is probably not the patient, but the attitudes from healthcare professionals indicating that education of the providers of lifestyle interventions is needed.
10. Summary

10.1 English

Introduction
The large majority of risk factors during surgery are not as preventable as daily smoking and risky alcohol drinking. Smoking is the major risk factor for developing bladder cancer and about 60 % of patients undergoing radical cystectomy (RC) develop one or more postoperative complications. The risk of postoperative complications is significantly reduced after a 4-8 week preoperative smoking or alcohol cessation intervention. Evidence for perioperative smoking and alcohol cessation interventions in radical cystectomy pathways is missing.

Aims
The aims of this thesis were 1) to determine if patients undergoing robot assisted radical cystectomy developed fewer complications and had a better health related quality of life compared to patients undergoing open radical cystectomy (study I), 2) to evaluate the effect of a perioperative smoking and alcohol cessation intervention in relation to radical cystectomy on postoperative complications – the STOP-OP study (study II) and 3) to explore how patients experienced the smoking and alcohol intervention in the STOP-OP study (study II).

Material and methods
In study I we carried out a systematic literature search followed by a systematic review and meta-analysis. Study II concerned a larger RCT, the STOP-OP study currently enrolling bladder cancer patients scheduled for RC being daily smokers or drinking > 20 units of alcohol per week. Patients in study II were randomised to the Gold Standard Programme for smoking cessation and the intervention group took part in five meetings in six weeks combined with free nicotine replacement therapy; patients in the control group received standard care. Part of study II was a qualitative study in which participants from the STOP-OP study were interviewed.

Results
In study I we included four randomised controlled trials involving a total of 239 patients. The evidence was of low to moderate quality. There was no significant difference between RARC and ORC in the number of patients developing complications within 30 or 90 days or in overall grade 3-5 complications within 30 or 90 days postoperatively, in length of stay or HRQoL.
Study II analysed data from 47 patients who were daily smokers. Adherence to the intervention was very high. The continuous abstinence rate was 57 % in the intervention group and 33 % in the control group, and unadjusted analyses were not significant. Adjusting for age and sex analyses showed a five times larger odds for smoking abstinence after the intervention.
In the qualitative part of study II eleven patients from the intervention group in the STOP-OP study were interviewed. The analysis showed that the smoking and alcohol cessation intervention was experienced as an integral part of bladder cancer surgery and that returning to everyday life was a barrier for continued smoking cessation/alcohol reduction.

**Conclusion**

The smoking and alcohol cessation intervention was well received by the participants. So far no significant difference in smoking cessation has been found between the two groups. Future data collection in the STOP-OP study will focus on the effect of the combined smoking and alcohol cessation intervention on postoperative complications as well as health-related quality of life.

**10.2 Dansk**

**Introduktion**

Størstedelen af de kirurgiske risikofaktorer er ikke så lette at forebygge som daglig rygning og storforbrug af alkohol. Rygning er den væsentligste risikofaktor for udvikling af blærekræft og ca. 60 % af de patienter, der får fjernet blæren ved radikal cystektomi (RC) udvikler en eller flere komplikationer. Ryge/alkohol stop 4-8 uger inden operation nedsætter signifikant risikoen for komplikationer. Evidens for perioperative ryge- og alkohol stop programmer i forbindelse med RC savnes fortsat.

**Formål**

Formålet med denne afhandling er 1) at afgøre om de patienter, der fik fjernet blæren ved hjælp af robotkirurgi udviklede færre komplikationer og opnåede en højere helbredsrelateret livskvalitet end de patienter, der gennemgik åben kirurgi (studie I) 2) at evaluere effekten af en perioperativ ryge-og alkohol stop intervention i forbindelse med RC på komplikationer – STOP-OP studiet (studie II) og 3) at undersøge hvordan patienterne oplevede at deltage i ryge- og alkohol stop interventionen i STOP-OP studiet (studie II).

**Materiale og metode**


**Resultater**

I studie I inkluderede vi fire randomiserede studier med ialt 239 patienter. Kvaliteten af evidensen var lav til moderat. Der var ingen signifikant forskel på antal patienter med komplikationer indenfor 30 og
90 dage efter robot assisteret operation og åben operation, ej heller i det samlede antal grad 3-5 komplikationer indenfor 30 og 90 dage, i indlæggelsestid eller helbredsrelateret livskvalitet. Studie II analyserede data fra 47 patienter, der var daglige rygere. Adherence til møderne i interventionen var meget høj. Det kontinuerde rygestop var 57 % i interventionsgruppen og 33 % i kontrolgruppen, i de ujusterede analyser var forskellen ikke signifikant. Når vi justerede for alder og køn, var chancen for rygestop fem gange større i interventionsgruppen.

**Konklusion**

Ryge- og alkohol stop interventionen blev modtaget godt af deltagerne. Indtil nu er der ikke påvist en signifikant forskel i rygestop mellem de to grupper. Fremtidige data fra STOP-OP studiet vil vise, om der er en effekt af en samlet ryge- og alkohol stop intervention på postoperative komplikationer og helbredsrelateret livskvalitet.
11. References


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12. Papers I-IV

12.1 Paper I
12.2 Paper II
12.3 Paper III
12.4 Paper IV