



REDUCING SURGICAL COMPLICATIONS IN NEWLY DIAGNOSED LUNG CANCER PATIENTS WHO SMOKE CIGARETTES

Ivana T. Croghan, PhD

Jeff Sloan, PhD

Alliance November 2015

Learning Objectives

- *Describe why stopping smoking prior to surgery so important in the recovery*
- *List available options for stopping smoking*
- *Define study eligibility*
- *Describe the study flow*

Facts



- **234.2 million** annual major surgical procedures worldwide 3% major complications
 - 1.5% death – during or after surgery
- Smokers have an **OR of 1.2 to 1.6** for surgical complications compared to non-smokers
- And it is hard to find an ashtray in an operating theater

(Lancet 372:139-144, 2008)

Surgical Complications



<p>30-day mortality 1-year mortality Anastomotic leak Anesthesia-related respiratory complications Bleeding (transfusions >5 U) Coma (>24 hours) Deep venous thrombosis/thrombophlebitis Failure to wean from the ventilator ICU readmission Impaired bone healing Implant loss (breast reconstruction)</p>	<p>Increased postoperative pain Renal insufficiency/failure Return to operating room Sepsis/septic shock Stroke/cerebral accident Surgical infection (organ space) Surgical site infections Urinary tract infections Increased postoperative surgical stay Increased scarring and asymmetry Intubation (unplanned)/re-intubation Lower rates of successful digital replantation (microsurgery) Myocardial infarction</p>	<p>Pneumonia Prolonged intubation Prolonged ventilator support Pulmonary complications Pulmonary embolism Reduced skin flap survival Vascular complications Vein graft failure Venous thromboembolism Ventilator (>48 hours) Wound healing (delayed) Wound infection (sternal) Wound infections (superficial and deep)</p>
---	--	---

Khullar & Maaj. Surgeons(3):418-426, 2012

Benefits of Not Smoking are Immediate...

- 20 minutes
 - Heart rate and blood pressure drop
- 8 hours
 - Carbon monoxide in the blood stream is normalized
 - Improvement of myocardial oxygen supply
- 24 hours
 - Chance of sudden heart attack decreases
 - Increased exercise capacity
- 48 hours
 - Ability to taste and smell is greatly improved
- 1 week
 - Physical withdrawal symptoms end

Rodrigo et al, Anesth Prog 47: 143-50, 2000

...And Increase Over Time

- 3-9 months
 - Lung function increases up to 30%
 - Circulation improves
 - Cilia regain function
- 1 year
 - Risk of coronary artery disease is halved
- 5 years
 - Risk of stroke and cervical cancer is that of a nonsmokers
 - Risk of cancer of the mouth, throat, esophagus and bladder are halved
- 10-15 years
 - Risk of lung cancer is halved
 - Risk of cancer of the larynx and pancreas decreases
 - Risk of coronary heart disease is that of a never smoker

Tobacco Use Interventions 101

- They work (*when accessible*)
 - Efficacy increases with intensity
 - *Even brief advice to quit by a clinician works*
 - The most effective interventions combine behavioral and pharmacologic therapies and ~double the odds
- They take many forms
 - Delivery by clinicians
 - Tobacco Treatment Programs
 - Remote delivery techniques
 - “Quitlines”
 - Web-based, social media, apps



Approved Pharmacotherapy

- Nicotine Replacement
 - Nicotine Patch
 - Nicotine Gum
 - Nicotine Spray
 - Nicotine Inhaler
 - Nicotine Vaccine
- Bupropion
- Varenicline

The Real Barriers to Intervention

“I don’t know how”

“I don’t have time”

“It’s not my job”

Smokers expect us to talk about how their smoking affects surgery

- Essentially all smokers are aware of general health hazards
 - Most are not aware of how it might affect their surgery – **and want to know!**
- They want **information** and **options**
- Almost all will **not** be offended if you discuss their smoking...
- But they do not want a sermon, they want help
- “Temporary” abstinence attractive to many

Warner et al, Am J Prev Med 2008

What should we do for smokers who need surgery?

- **ASK** - assess tobacco use at every visit
- **ADVISE** - strongly urge all tobacco users to quit
- **REFER** – To a tobacco quitline or other resources

http://www.treatobacco.net/en/page_224.php

ASK every patient about tobacco use

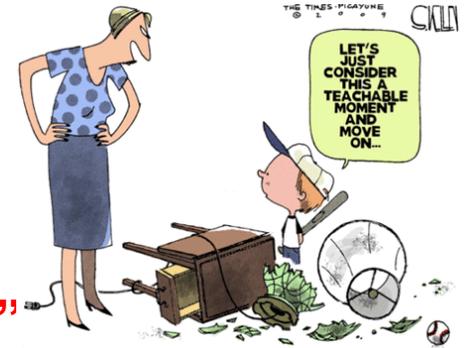
- Ask even if you already know the answer
 - Reinforces message that you as a provider think that their tobacco use is significant

ADVISE all smokers to quit

- Quit for as long as possible before and after surgery
 - Day of surgery especially important: fast from both food and cigarettes
- Benefits of quitting to wound healing, heart, and lungs
- Great opportunity to quit for good
 - Many people do not have cravings
 - Need to be smoke free during inpatient recovery

Teachable Moment

“Opportunities in which patients have enhanced susceptibility to interventions on unhealthy behaviors”



- Use of teachable moments can occur at:
 - Upcoming surgery (8% - 25% success)
 - office visits (2–10% success)
 - notification of abnormal test results (7–21% success)
 - pregnancy (10–60% success)
 - hospitalization and disease diagnosis (15–78% success).
- The steps in using a teachable moment to help smokers quit smoking include:
 - simple physician advice to quit
 - brief behavioral interventions provided by physicians or other clinicians
 - pharmacotherapy

McBride et al *Health Edu Res* 2003; 18 (2):156-170

Warner et al *Anesth. Analg.* Aug 2005;101(2):481-487

Simons et al *Patient Educ. Couns.* Dec 2009;77(3):398-403

Lee et al *Anesth Analg* 2015; 120:582-7

REFER smokers to quitlines or other resources

- What are quitlines?
 - Quitlines are free
 - Talk with a specialist, not a recording
 - Free stop smoking medications may be available
 - Can call anytime, even after surgery
 - Can help you stay off cigarettes even if you have already quit
- Can also use proactive fax referral



http://www.treatobacco.net/en/page_407.php

In Summary

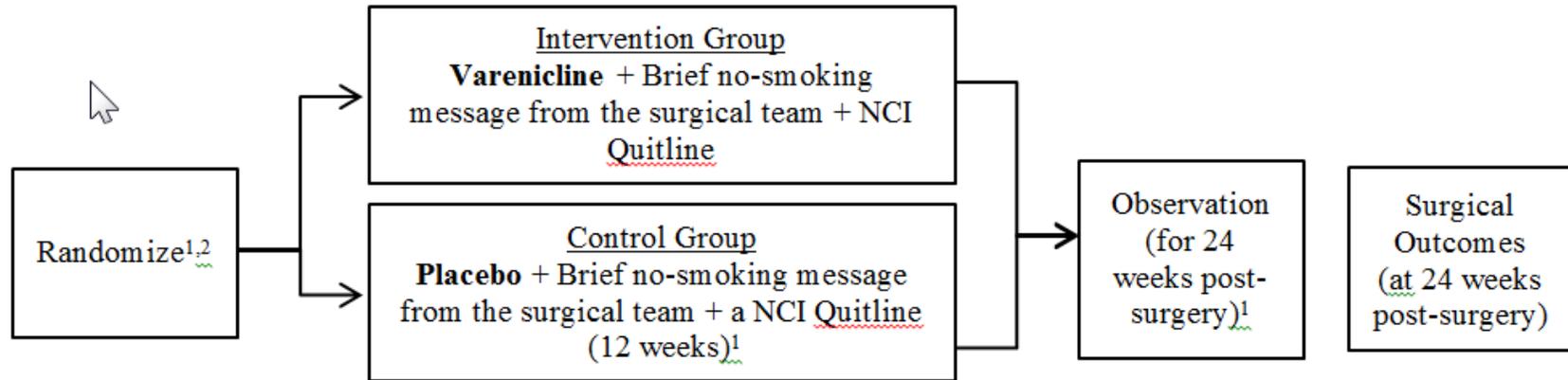
- Within 4-8 weeks, smoking cessation can **reverse** some of the **effects** caused by years of smoking.
- Available evidence suggests that major surgery for a smoking-related illness can serve as a significant and effective **teachable moment** for smoking cessation.
- A study of 5498 individuals enrolled in the Health and Retirement Study demonstrated that older individuals (≥ 50 years) are more likely to quit smoking after a major medical procedure.
- The **steps** in helping smokers quit smoking during their TM include:
 - simple physician advice to quit,
 - brief behavioral interventions provided by physicians or other clinicians,
 - Pharmacotherapy

Anesth. Analg. Aug 2005;101(2):481-487
Patient Educ. Couns. Dec 2009;77(3):398-403
Anesthesiology. Jan 2010;112(1):102-107

Protocol in Development

- Protocol Draft #2 submitted Sept 18, 2015
- Consent form developed
- Pfizer has agreed to supply drug/placebo
- Plan for training of study team for the “teachable moment” in development
- CRFs in progress
- Medidata Rave – in development

Study Schema



- 1 Tobacco use will be assessed prior to registration, at randomization, and every six weeks during treatment and observation until 24 weeks after surgery.
- 2 **Please note:** Baseline is at the time the surgical message is discussed with the cancer patient. Surgery must occur after the target quit date (TQD) defined at baseline and can be performed no sooner than 10 days after randomization and no more than twelve weeks after randomization.

Overall Objective

To assess the effect of smoking cessation treatment on **surgical complications, QOL, and post-operative care.**



Specific Aims:

Primary

- To determine if varenicline, when added to a behavioral intervention consisting of a brief clinician-delivered intervention with tobacco quitline follow-up, decreases postsurgical complications through 24 weeks after surgery in lung cancer patients who undergo surgery and are motivated to stop smoking.

Secondary Objectives

- To compare changes from baseline to 12 and 24 weeks after surgery in the patient **quality of life** (LASA10) domains between the intervention (varenicline) and control group (placebo).
- To compare changes from baseline to 4, 8, 12 and 24 weeks after surgery in the patient quality of life related domains (**LASA**) for the **PHQ-9** and **SEQ12** between the intervention and control groups.
- To compare the proportion of patients 12 weeks and 24 weeks after surgery who **endorse** (“Was It Worth It”) each treatment (intervention vs. control groups).
- To compare **post-operative care** (as measured by length of hospital and high dependency unit stay) between the intervention and control groups.
- To compare **treatment adherence** between the intervention and control groups.
- To compare **rates of smoking abstinence** between the intervention and control groups.

Correlative Science Objectives

- To evaluate the predictive role of the nicotinic receptor gene cluster (*CHRNA5-CHRNA3-CHRNA4*) and *CYP2A6* genotypes in smoking cessation among lung cancer patients undergoing surgery.
- To evaluate the potential moderating effect of these cessation-relevant genotypes on smoking cessation treatment between the intervention and control groups.

Informal considerations for subject enrollment

- Diagnosis of Lung Cancer and a surgical consult
- No Psychiatric illness which would prevent the patient from giving informed consent.
- No Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients who cannot swallow oral formulations of the agent.
- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

Stratification Factors

Patients will be stratified into three groups based on the type of resection performed:

- pneumonectomy,
- lobectomy or bilobectomy,
- sublobar resection (segmentectomy or wedge resection).

Treatment Assignments and Blinding

Patients will be randomized 1:1 to receive one of two treatments:

- Intervention Group: Participants will receive **varenicline** plus a brief no-smoking message from the surgical team and behavioral support provided by a telephone smoking quitline (NCI's 1-877-44U-QUIT) for 12 weeks.
- Control Group: Participants will receive **placebo** plus a brief no-smoking message from the surgical team and behavioral support provided by a telephone smoking quitline (NCI's 1-877-44U-QUIT) for 12 weeks.

Teachable Moment Training

- Surgeons and designated members of the surgeon's team will be trained and educated in the basics of smoking cessation counseling and delivery of the No-Smoking message to the surgical oncology patient.
- The training will be conducted via Webinars for convenience of the site study teams, and based upon a validated approach to clinician-delivered tobacco use intervention (Warner et al, Anesthesiology 114:847-855, 2011).
- A standardized script of key speaking points will be developed and utilized by all participating surgical teams.
- Study subjects will be provided with a folded flyer which will re-inforce the surgical team message as well as the quitline phone number
- All training will be documented and each site must have this training prior to study start up – for consistency.

Study Calendar

	Consent /screen*	Baseline	Day of Surgery**	Week 6	Week 12	Week 18	Week 24
Med Hx/PE	X	X					
Screen/ registration	X						
AE/Con Meds		X					
Quit Message		X					
Quitline		X					
Study Med		X	X	X			
PHQ-9	X			X	X		X
Tobacco Use Assessment	X	X	X	X	X	X	X
SEQ-12		X		X	X		X
LASA		X	X	X	X		X
Saliva		X	X	X	X		X
Blood		X					



Questions

croghan.ivana@mayo.edu

jsloan@mayo.edu