



## Treatment of Tobacco Use in Lung Cancer

### Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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**Background:** Continued tobacco use in the setting of lung cancer management is frequently confounding and always of critical importance. We summarized the published literature concerning the management of tobacco dependence in patients with lung cancer and offer recommendations for integrating dependence treatment into ongoing oncologic care.

**Methodology:** MEDLINE, Embase, CINAHL, PsychINFO, and the Cochrane Collaborative databases were searched for English language randomized clinical trials, cohort studies, case-control studies, secular trend analyses, and case series relevant to the a priori identified clinical questions. Evidence grading, integration, and genesis of recommendations followed the methods described in "Methodology for Development of Guidelines for Lung Cancer" in the American College of Chest Physicians Lung Cancer Guidelines, 3rd ed.

**Results:** We describe the approach to tobacco dependence in patients with lung cancer at various phases in the evolution of cancer care. For example, among patients undergoing lung cancer screening procedures, we recommend against relying on the screening itself, including procedures accompanied solely by self-help materials, as an effective strategy for achieving abstinence. Among patients with lung cancer undergoing surgery, intensive perioperative cessation pharmacotherapy is recommended as a method for improving abstinence rates. Cessation pharmacotherapy is also recommended for patients undergoing chemotherapy, with specific recommendations to use bupropion when treating patients with lung cancer with depressive symptoms, as a means of improving abstinence rates, depressive symptoms, and quality of life.

**Conclusions:** Optimal treatment of lung cancer includes attention to continued tobacco use, with abstinence contributing to improved patient-related outcomes at various phases of lung cancer management. Effective therapeutic interventions are available and are feasibly integrated into oncologic care. A number of important clinical questions remain poorly addressed by the existing evidence.

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**Abbreviations:** ACCP = American College of Chest Physicians; CBT = cognitive behavioral therapy; C-SHIP = Cognitive-Social Health Information-Processing; LDCT = low-dose CT; NRT = nicotine replacement therapy; PICO = population, intervention, comparator, outcome; QOL = quality of life; RR = relative ratio; RT = radiation therapy; SR = sustained-release; VTA = ventral tegmental area

#### SUMMARY OF RECOMMENDATIONS

**3.1.1.1. We recommend that current smokers undergoing low-dose CT screening be provided with cessation interventions that include counseling and pharmacotherapy (Grade 1B).**

*Remark:* The act of screening alone is insufficient to promote smoking cessation.

*Remark:* The use of self-help materials is insufficient for achieving an increased rate of smoking abstinence.

**3.1.1.2. Among current smokers with demonstrated smoking related pulmonary disease we recommend providing intensive cessation interventions (Grade 1B).**

**3.2.1.1. Among lung cancer patients undergoing surgery, we recommend perioperative cessation**

pharmacotherapy as a method for improving abstinence rates (Grade 1B).

**3.2.1.2. Among lung cancer patients undergoing surgery for whom pharmacotherapeutic support is either contraindicated or refused, we suggest cessation counseling alone during the perioperative period (Grade 2C).**

**3.2.1.3. Among lung cancer patients undergoing surgery, the timing of cessation does not appear to increase the risk of post-operative complications; we suggest that cessation interventions be initiated in the pre-operative period (Grade 2C).**

*Remark:* Small observed effect sizes and limitations in experimental design do not justify delaying surgical procedures in favor of longer abstinence duration.

**3.2.1.4. For lung cancer patients attempting cessation in conjunction with surgical interventions, we recommend initiating counseling and pharmacotherapy at the outset of surgical intervention (Grade 1B).**

*Remark:* There is substantial evidence suggesting that reliance on short, low intensity cessation interventions such as advice to quit does not improve abstinence outcomes.

**3.3.1.1. Among lung cancer patients undergoing chemotherapy, we recommend cessation inter-**

**ventions that include counseling and pharmacotherapy to improve abstinence rates (Grade 1B).**

**3.3.1.2. Among lung cancer patients with depressive symptoms, we suggest cessation pharmacotherapy with bupropion as a method to improve abstinence rates, depressive symptoms, and quality of life (Grade 2B).**

**3.3.1.3. Among lung cancer patients for whom pharmacotherapeutic support is either contraindicated or refused, we suggest cessation counseling alone as a method to improve abstinence rates (Grade 2C).**

**3.4.1.1. Among lung cancer patients undergoing radiotherapy, we recommend cessation interventions that include counseling and pharmacotherapy (Grade 1C).**

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Continued tobacco use despite a diagnosis of lung cancer remains a frustrating circumstance for both patient and physician. The seriousness of the illness presents an apparent non sequitur, wherein the patients' willingness to undergo invasive or uncomfortable treatment and their obvious desire to prolong life do not seem to align with their apparent unwillingness to discontinue tobacco use. Rather than representing a deficit in desire, however, this paradox may instead be a dramatic manifestation of disordered motivation functions of the brain.<sup>2</sup> In essence, abnormally amplified, but maladaptive, motivations become an incredibly strong obstacle to achieving the more desirable, adaptive behaviors.

Patients trapped within this paradox face significant negative consequences. Understandable feelings of shame, guilt, and resignation might be compounded by familial disapproval and compromised social support during a trying illness. Depression and other psychiatric disorders are also in no short supply among patients with cancer who continue to smoke.<sup>3</sup> A comprehensive approach to improving lung cancer survival and quality of life (QOL) should also, then, include strategies for effectively attending to this difficult issue.<sup>4</sup>

### *Why Would Patients With Cancer Continue to Smoke?*

Nicotine addiction is simultaneously common, powerful, and deadly. Unfortunately, it remains poorly understood within most sectors of our society. Nicotinic acetylcholine receptors are located in all areas of the mammalian brain, but the main effectors of addiction are concentrated in sites that are of critical importance to basic survival functions. Nicotine drives continued smoking by activating an instinctual

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“appetitive” state, motivating goal-directed behaviors and cognitive processes aimed at resolving barriers to gratification.<sup>5</sup> A key component of the circuitry of the mesolimbic system is a collection of nerve cells that originate in the ventral tegmental area of the brain (VTA). Neurons of the VTA send projections to the nucleus accumbens, a structure implicated as the brain’s main locus of reward and central to the development of addiction. The VTA is populated by neurons that respond to salient “safety/threat” stimuli from the outside world, including, for example, food, sex, and social interaction. The inputs in the VTA are predominantly cholinergic and, importantly, primarily nicotinic.<sup>6,7</sup> Because of this, nicotine has the ability to act as an exogenous ligand that reliably activates endogenous cholinergic receptors in the survival centers of the brain, creating a powerful but incorrect “imposter” safety signal. In this way, nicotine exerts its influence by hijacking the most fundamental survival functions of the brain, capable of compelling behavior even more profoundly than the “classic” drugs of abuse, including cocaine, amphetamine, and morphine.<sup>8</sup> When patients face the possibility of abstinence, they face the instinctive equivalent of a threat to survival, even though they may intellectually understand abstinence to be the rational, logical path toward ensuring survival.

The physical effects of nicotine on the brain’s survival structures are obdurate. Although clinicians may understand addiction to be an illness characterized by remission and relapse, it is always painful to watch a desperate patient succumb to the long reach of compulsive behavior. The conceptualization of addiction as a chronic illness is not merely a convenient framework for discussion; nicotine exposure promotes changes in gene expression, protein transcription, receptor density, and neuronal arborization patterns that may never be fully reversed following discontinuation.<sup>9</sup> For example, chronic nicotine exposure causes sustained activation of cAMP response element-binding protein, which enhances expression of its target genes, strengthening neuronal relationships within the circuit. Another transcription factor,  $\Delta$ FosB, appears to be extraordinarily stable, exerting its control over gene expression for months following nicotine exposure.<sup>9,10</sup> These factors confer persistence to learned associative connections, and although the strength of connections may gradually diminish in response to prolonged abstinence, they may never be fully divorced, amplifying the patient’s visceral response to cues for many years after the last cigarette.

### *Lung Cancer Specialists Have an Ethical Responsibility to Act*

The early days of tobacco control were marked by significant reductions in tobacco use and have been

described as one of the 10 greatest achievements in public health in the 20th century. Since then, however, and despite significant state-to-state variability, overall adult prevalence appears to have reached a plateau at approximately 20%.<sup>11</sup> Even in states with well-developed tobacco control policies, like California and New York, trends suggest that sustained efforts will be required to further reduce the prevalence of tobacco use.<sup>12</sup> The Institute of Medicine conducted a study of tobacco use in the United States and published a report in which the authors concluded that “substantial and enduring reductions in tobacco use cannot be achieved by simply expecting past successes to continue.”<sup>13</sup> Although policy and environmental influence variables appear to have a significant impact on some cessation outcomes when assessed independently, important relationships become nonsignificant when the modeling includes a full set of policy and environmental variables.<sup>14</sup> In particular, surveillance data of lung cancer incidence and risk exposure over the past several decades suggest a weak correlation between annual budgets for tobacco control and the rate of change in tobacco prevalence.<sup>15</sup> These observations suggest that, although a number of policies may have a general influence on cessation outcomes, their relationship to the patient’s experience of tobacco dependence is, at best, complex and indirect. Who better than lung cancer specialists to advocate for more effective smoking cessation strategies and to implement treatment guidelines in their practice that will directly improve cancer outcomes among their patients?

### *Isn’t the Horse Out of the Barn?*

Many patients with newly diagnosed lung cancer are smoking at the time of diagnosis.<sup>16</sup> Many continue to smoke even after their diagnosis, demonstrating their strong tobacco dependence.<sup>17</sup> Fortunately, survival rates for lung cancer continue to improve; unfortunately, people who continue to smoke after their lung cancer diagnosis nearly double their risk of dying.<sup>18</sup> A growing body of evidence suggests that tobacco use treatment after a lung cancer diagnosis is linked to more effective cancer treatment and a better prognosis. As patients with lung cancer experience longer survival times, they are more likely to benefit from the QOL improvements associated with abstinence. After quitting, patients with lung cancer report decreased fatigue and shortness of breath, improved performance status and appetite, as well as improved cognitive function, psychologic well-being, and self-esteem—outcomes generally considered to be of nontrivial importance.<sup>17</sup> Abstinence appears to decrease the risk of synchronous primary lung cancers, metachronous lung cancers among small cell lung cancer survivors, and second

primary tumors.<sup>19-22</sup> Compared with the general population, the risk of all second cancers was increased 3.5 times among patients who continued to smoke.<sup>20</sup> This risk was highest among patients who received chest radiotherapy, with a relative risk of 21 compared with nonsmokers.

### *Do Patients With Lung Cancer Even Want to Stop Smoking?*<sup>9</sup>

Most patients with cancer who smoke at the time of diagnosis attempt to quit without formal treatment.<sup>3</sup> Although depressive symptoms and low quitting self-efficacy are common in this patient group, patients neither perceive disadvantages to quitting nor hold fatalistic beliefs. Patients with lung cancer were significantly less likely to decline treatment than a reference group with head and neck cancer.<sup>23</sup> Although patients with lung cancer frequently cite a preference for quitting without professional assistance, this may be a manifestation of guilt, depression, or poor self-efficacy. Rather than representing a rationale for allowing patients with cancer to proceed without direction, this finding should trigger motivational interventions aimed at improving self-efficacy and facilitating treatment engagement.<sup>24</sup>

### *Rationale for This Article*

If the biology of nicotine addiction manifests as a strong, ineluctable, obdurate, visceral motivation to smoke, then we are obligated to reexamine our interpretation of patients' demonstrated reluctance to quit.<sup>2</sup> If abstinence has a profound effect on cancer outcomes and QOL, and if environmental interventions unreliably support abstinence, then passive approaches to achieving this outcome are insufficient. Finally, if patients with lung cancer are likely to both attempt abstinence and fail to achieve abstinence on their own, then we are obligated to provide professional assistance to help them achieve the best outcomes possible. To help lung cancer professionals reach these goals, this article is organized into two relevant sections. In the first, a brief summary of the evidence-based guideline recommendations published by the US Department of Health and Human Services is presented. It is infeasible to reproduce *Treating Tobacco Use and Dependence: 2008 Update* in its entirety; those unfamiliar with this seminal work are encouraged to visit the Surgeon General's website (<http://www.surgeongeneral.gov/tobacco/>) for a free copy of this extensive body of work, including free worksheets and handouts for patients.<sup>25</sup> In the second section, evidence in support of critical treatment questions specific to the lung cancer population is presented, along with specific treatment

recommendations and evidence grades. Where identified, inadequacies in the evidence base are outlined, and suggestions for future research directions are offered.

## 1.0 GENERAL PRINCIPLES OF TREATING TOBACCO USE AND DEPENDENCE

### *1.1 Tobacco Use Status of All Patients Should Be Assessed and All Smokers Should Be Offered Treatment*

Clinic systems designed to identify the tobacco use status of patients should be implemented, integrated into the flow of the patient's visit experience, and updated routinely to accurately reflect longitudinal change. One strategy for achieving this aim is to expand vital sign assessment to include current tobacco use status. Clear descriptors, such as current, former, or never smoker, can be used for documentation. For patients identified as current smokers, reliance on self-help materials is generally ineffective. Cancer diagnosis has been termed a "teachable moment," and oncologists have a prime opportunity to capitalize on patients' motivation to quit smoking.<sup>26</sup> Physicians and their staff (eg, nurses, medical assistants, and so forth) should deliver clear and personalized advice to quit. This advice might include elements such as an offer of ongoing support, a referral to specialized tobacco treatment services, a discussion of the personal relevance of quitting (ie, the impact of continued smoking on cancer treatment and outcomes), education regarding the anticipated effect of pharmacotherapy on withdrawal symptoms and likelihood of abstinence, and referral to their state's free tobacco quit line (1-800-QUIT-NOW). Consider discussing past quit experiences—identify what worked and what did not during previous quit attempts. Build on past success. Identify the patient's perceived triggers and challenges, and offer reassurance that treatment will be ongoing and nonjudgmental.<sup>27</sup>

### *1.2 All Treatment Approaches Should Include Prescribed Pharmacotherapy and Counseling*

Pharmacotherapy for tobacco dependence is both effective and safe in a variety of populations, including those patients with cardiovascular disease. Tobacco dependence treatments are also highly cost-effective relative to interventions for other clinical disorders. Seven first-line medications reliably increase long-term smoking abstinence rates and include sustained-release (SR) bupropion, nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray, nicotine patch, and varenicline. Clinicians should also consider the use of certain combinations of medications identified



as effective in the guideline.<sup>25</sup> The anticipated effect size for each of the medication choices, both singly and in combination, are summarized in Figure 1. Although some of these therapies are available over the counter, many insurance plans provide benefit coverage if use is directed by prescription. Consequently, pharmacotherapy recommendations should be accompanied by a written prescription in all cases. Coverage for these treatments may require prior authorization or, in some cases, certification that the patient is receiving counseling. However, the increase in quit rates associated with use of these medications makes them worthy of the small additional effort. The highest quit rates are achieved by combining pharmacotherapy with counseling. Even in circumstances in which the clinical team is unable to provide smoking cessation counseling directly, patients should still be referred to a specialized tobacco treatment service, or to their state quit line, to augment the effectiveness of the prescribed medication.

### 1.3 Approach to Treatment Is Most Consistent With a Chronic Disease Model of Care

Given that the functional changes in neurophysiology associated with nicotine addiction are obdurate, the downstream behavioral manifestation of tobacco dependence must be considered chronic, with predictable periods of waxing and waning. Tobacco dependence is a disease that requires repeated intervention over time. In patients currently unwilling to make a quit attempt, or in those expressing a desire to proceed unassisted, the focus should be on motivational maneuvers that may increase the likelihood of future quit attempts, including nicotine sampling,<sup>28</sup> patch pretreatment,<sup>29</sup> and extended varenicline treatment prior to quit day.<sup>30</sup>

### 1.4 Tools and Resources

In addition to the excellent clinical resources that accompany the *Treating Tobacco Use and Dependence*:

FIGURE 1. [Section 1.2] Effect sizes of various pharmacotherapy cessation strategies on abstinence rates.<sup>25</sup>

Medication	No. of study arms	Estimated odds ratio (95% CI)	Estimated abstinence rate (%) (95% CI)
Placebo	80	Reference	13.8
<b>Monotherapies</b>			
Varenicline (2 mg/day)	5	3.1 (2.5–3.8)	33.2 (28.9–37.8)
Nicotine Nasal Spray	4	2.3 (1.7–3.0)	26.7 (21.5–32.7)
High-Dose Nicotine Patch <sup>a</sup> (>25 mg)	4	2.3 (1.7–3.0)	26.5 (21.3–32.5)
Long-Term Nicotine Gum (> 14 wks)	6	2.2 (1.5–3.2)	26.1 (19.7–33.6)
Varenicline (1 mg/day)	3	2.1 (1.5–3.0)	25.4 (19.6–32.2)
Nicotine Inhaler	6	2.1 (1.5–2.9)	24.8 (19.1–31.6)
Clonidine	3	2.1 (1.2–3.7)	25.0 (15.7–37.3)
Bupropion SR	26	2.0 (1.8–2.2)	24.2 (22.2–26.4)
Nicotine Patch (6–14 weeks)	32	1.9 (1.7–2.2)	23.4 (21.3–25.8)
Long-Term Nicotine Patch (>14 wks)	10	1.9 (1.7–2.3)	23.7 (21.0–26.6)
Nortriptyline	5	1.8 (1.3–2.6)	22.5 (16.8–29.4)
Nicotine Gum (6–14 weeks)	15	1.5 (1.2–1.7)	19.0 (16.5–21.9)
<b>Combination therapies</b>			
Patch (long-term; >14 wks) + <i>ad lib</i> NRT (gum or spray)	3	3.6 (2.5–5.2)	36.5 (28.6–45.3)
Patch + Bupropion SR	3	2.5 (1.9–3.4)	28.9 (23.5–35.1)
Patch + Nortriptyline	2	2.3 (1.3–4.2)	27.3 (17.2–40.4)
Patch + Inhaler	2	2.2 (1.3–3.6)	25.8 (17.4–36.5)
Patch + 2 <sup>nd</sup> generation antidepressants (paroxetine, venlafaxine)	3	2.0 (1.2–3.4)	24.3 (16.1–35.0)

NRT = nicotine replacement therapy; SR = sustained release.

<sup>a</sup>These included both standard or long-term duration.

2008 Update guideline, a number of other agencies have made clinical and educational tools available. The ACCP has assembled an extensive, yet practical, collection of clinical tools, decision algorithms, coding guidelines, and other resources, useful in streamlining tobacco treatment practice. Although not itself a clinical guideline, *The ACCP Tobacco Dependence Treatment ToolKit*<sup>31</sup> facilitates practical management by incorporating elements of the US Public Health Service guideline into straightforward, easily adoptable clinical tools. The material is free and available at <http://tobaccodependence.chestnet.org>.

## 2.0 METHODS

A description of the methods used for the third edition of the ACCP Lung Cancer Guidelines can be found in Lewis et al.<sup>1</sup> "Methodology for Development of Guidelines for Lung Cancer" in the ACCP Lung Cancer Guideline.<sup>1</sup> To develop this article, a literature review was conducted to identify available evidence within several databases, including MEDLINE, Embase, CINAHL, PsychINFO, and the Cochrane Collaborative. Google Scholar was also used to identify relevant reviews and articles that may have contained references not retrieved by the database search. The search was structured around the following population, intervention, comparator, outcome (PICO) questions (see also Table S1):

1. Among patients who smoke, what is the impact of efforts to screen for the presence of lung cancer on smoking behavior?
2. Among patients with lung cancer undergoing surgery, what is the best approach to smoking cessation?
3. What is the best approach to smoking cessation among patients with lung cancer undergoing chemoradiotherapy?
4. What is the impact of smoking cessation on patients with lung cancer undergoing radiation therapy (RT)?

Expanded search terms were used to identify the evidence, including terms such as cancer, neoplasm, lung cancer, lung nodule, nicotine, smoking, smoking cessation, tobacco, tobacco dependence, diagnosis, chemotherapy, surgery, radiation, lung cancer

treatment, and lung cancer screening. Search results were limited to those articles published from 1985 to present, relating to human subjects, and available in English. Initially, 989 unique citations met our search criteria. Following title screening for relevance, 568 unique relevant articles remained as candidates for inclusion in the evidence base, available for review by the authors. Study designs retained for this guideline included randomized controlled trials, cohort, case-control, secular trend, and case series. Each of the articles meeting inclusion criteria was then reviewed and mapped to the appropriate PICO question. An additional eight articles were identified by the authors through review of reference lists of primary reports and applicable review articles. Overall, 531 articles did not meet inclusion criteria, were found to be noninformative, or were no longer available, leaving a total of 37 articles for inclusion in the final evidence tables.

## 3.0 CLINICAL QUESTIONS AND RECOMMENDATIONS

### 3.1 Among Patients Who Smoke, What Is the Impact of Efforts to Screen for the Presence of Lung Cancer on Smoking Behavior?

Interest in low-dose CT (LDCT) scanning as a lung cancer screening modality has been accompanied by interest in using the screening experience as a teachable moment for nicotine dependence intervention. Because of the direct relevance of smoking to lung cancer, and because of the serial nature of screening protocols, there has been considerable interest in understanding how smoking behaviors may be affected in this population. Although it is feasible that a positive LDCT scan result may motivate quit attempts, there is a converse concern that negative LDCT scan results may reinforce smoking behavior or even lead to relapse among recent quitters.

Four of the single-arm LDCT scanning studies and two randomized lung cancer screening trials performed in the last 2 decades examine the effect on smoking behavior (Fig 2, Table S2).<sup>32-39</sup> Although the

FIGURE 2. [Section 3.1] LDCT screening and smoking behavior.

First Author	N Total	% Men	Cessation Intervention	% Tobacco use at Baseline		% Quit Attempt		% Abstinence		% Relapse in former smokers	
				LDCT	Contr	LDCT	Contr	LDCT	Contr	LDCT	Contr
Schnoll <sup>32</sup>	55	0	Counseling	100	-	-	-	16 <sup>a</sup>	-	-	-
Cox <sup>33</sup>	1475	53	None	61	-	-	-	14 <sup>b</sup>	-	10	-
Clark <sup>34</sup>	85	54	Internet resources	61	-	68	-	5 <sup>b</sup>	-	-	-
	86	48	Self-help materials	61	-	48	-	10 <sup>b</sup>	-	-	-
Ashraf <sup>35</sup>	4104	55	Limited counseling	75	77	-	-	11 <sup>b</sup>	10 <sup>b</sup>	10 <sup>c</sup>	11 <sup>c</sup>
Styn <sup>36</sup>	2094	49	Limited counseling	100	-	59	-	16 <sup>b</sup>	-	-	-
Anderson <sup>37</sup>	2083	45	Limited counseling	35	-	-	-	29 <sup>d</sup>	-	4 <sup>e</sup>	-
MacRedmond <sup>38</sup>	449	---	Limited counseling	69	-	-	-	19 <sup>f</sup>	-	2	-
van der Aalst <sup>39</sup>	1284	100	Cessation brochure	91	78	-	-	14 <sup>f</sup>	16 <sup>f</sup>	-	-

Contr = control; LDCT = low-dose CT scan.

<sup>a</sup>Abstinence rate at 1 mo of follow-up.

<sup>b</sup>Abstinence rate at 1 y of follow-up.

<sup>c</sup>Relapse rate at 1 y of follow-up.

<sup>d</sup>Prolonged abstinence rate.

<sup>e</sup>Relapse rate at 6 y of follow-up.

<sup>f</sup>Abstinence rate at 2 y of follow-up.

studies used a variety of abstinence definitions, two reported rates of abstinence during a 1-year follow-up period ranging from 14% to 16%. The observed rates of new abstinence among smokers who underwent LDCT scan were noted to be higher than the predicted background rate in the general population; however, lack of a comparator group makes it difficult to estimate the true effect of CT scan screening on behaviors.<sup>33,36</sup> In general, there appeared to be a relationship between increasing suspicion of malignancy and an increased likelihood of smoking cessation, but this effect may diminish with time following the initial positive screening result.<sup>36,37</sup> Relative to no referral for tobacco use treatment, patients with low-suspicion CT scan results were more likely to make a quit attempt but not more likely to be abstinent at 1 year.<sup>36</sup> In one study, patients were followed for a 6-year period; there was no detectable increase in relapse among individuals with consistently negative screening compared with those with a positive, but noncancer, screening result.<sup>37</sup>

Several studies have been done evaluating the effect of active cessation counseling done in conjunction with cancer screening. In general, the counseling interventions used have been limited to self-help materials and referral to telephone counseling services.<sup>32,34,35,39</sup> Unfortunately, limited interventions have demonstrated only modest benefit as an adjunct to cancer screening. For example, in the NELSON (Dutch Belgian Randomised Lung Cancer Screening) trial,<sup>39</sup> all active smokers received a standard smoking cessation brochure or a questionnaire by which participants could request cessation information, whereas all smokers enrolled in the Danish Lung Cancer Screening Trial<sup>35</sup> received minimal smoking cessation counseling (<5 min) at each annual visit. Both studies failed to demonstrate an improvement in abstinence rates among subjects who underwent screening compared with those in the control arms.

In the only randomized study of brief counseling methods, 171 smokers undergoing lung cancer screening were assigned to receive either standard self-help materials or written, Internet-based resource materials. This study used a 7-day point prevalence measure of abstinence at 1 year following the screening test; although there were more cessation attempts in the group receiving Internet-based resources (68% vs 48%,  $P = .01$ ), both interventions resulted in similarly poor abstinence rates at 1 year (10% vs 5%,  $P = .166$ ).<sup>34</sup>

Another strategy has been to focus smoking cessation efforts on patients at elevated risk for lung cancer, including those with airway obstruction or prior asbestos exposure (Table S3).<sup>40-42</sup> In the Lung Health Study, 5,887 middle-aged volunteers with asymptomatic airway obstruction were randomized to either usual care or a 10-week program of group coun-

seling using behavior modification and nicotine gum. At 5 years, 22% of the intervention group had stopped smoking compared with 5% of the usual care group.<sup>41</sup> In the Step2quit trial, 571 participants underwent spirometric assessment and were randomized to receive their results either in terms of "lung age" or as the raw FEV<sub>1</sub>.<sup>40</sup> Both groups were advised to quit smoking and received referral to local cessation services. Quit rates were significantly higher in the lung age arm (14% vs 6%). Interestingly, in either group, those individuals with high spirometric age were no more likely to have quit when compared with those with normal spirometric age. Finally, in a study of 55 asbestos workers randomized to receive either usual care or telephone counseling plus pharmacologic therapy (nicotine replacement therapy [NRT] and/or bupropion), cessation rates at 6 months were higher in the intervention arm (17% vs 7%), but this difference was not statistically significant.<sup>42</sup>

In summary, the data regarding the effect of lung cancer screening on cessation rates and abstinence rates are limited; however, there is no evidence that either screening itself or the finding of a nonmalignant lesion has a substantial effect on cessation rates, even when accompanied by the relatively low-intensity counseling models most often associated with screening. There is some limited evidence that more intense counseling or combining this with pharmacotherapy can increase cessation rates in populations at high risk or in individuals diagnosed with smoking-related lung disease.

### 3.1.1 Recommendations

**3.1.1.1. We recommend that current smokers undergoing LDCT screening be provided with cessation interventions that include counseling and pharmacotherapy (Grade 1B).**

*Remark:* The act of screening alone is insufficient to promote smoking cessation.

*Remark:* The use of self-help materials is insufficient in achieving an increased rate of smoking abstinence.

**3.1.1.2. Among current smokers with demonstrated smoking related pulmonary disease we recommend providing intensive cessation interventions (Grade 1B).**

### 3.2 Among Patients With Lung Cancer Undergoing Surgery, What Is the Best Approach to Smoking Cessation?

Many patients with newly diagnosed lung cancer will be considered for surgical interventions. Generally, current smoking is considered a significant risk

factor for the development of postoperative complications following many different types of surgery. However, because smoking cessation can temporarily increase mucous production, concerns persist over whether cessation immediately prior to thoracic surgery may paradoxically *increase* risk of perioperative pulmonary complications. An extensive general surgical literature exists describing the impact of preoperative cessation interventions on long-term abstinence and the relationship between cessation and the risk of perioperative complications. Readers interested in the topic of smoking cessation and general surgical risk are referred to a recent Cochrane Database review of the subject.<sup>43</sup> The Cochrane authors conclude that interventions that begin 4 to 8 weeks before surgery, include weekly counseling, and use NRT are most likely to have an impact on long-term smoking cessation and a beneficial effect on complication rates.

Pulmonary resection following lung cancer diagnosis represents a special case of potential operative morbidity, for which guidance on questions of smoking cessation is limited. Although cessation interventions prior to lung cancer surgery are encouraged by many providers, significant questions regarding the most appropriate approach remain open. Several studies have evaluated the role of preoperative smoking cessation on the subsequent incidence of complications in patients with lung cancer and include some assess-

ment of the impact of timing (Fig 3, Table S4).<sup>44-48</sup> These studies varied in the definitions used for smoking status and in the outcomes included as postoperative complications but appear to demonstrate that nonsmokers had lower hospital mortality and fewer complications than any of the other groups. In a case-control analysis of 7,990 primary resections for lung cancer, the risk of hospital death and pulmonary complications after lung cancer resection were increased by smoking.<sup>44</sup> Compared with never smokers, the risk-adjusted OR for pulmonary complications following lung resection was no longer statistically significantly different for smokers who had quit at least 14 days prior to surgery. Barrera et al<sup>45</sup> used an even more aggressive definition of recent quitters, including smokers who quit at least 7 days prior to surgery. They found that there was no paradoxical increase in pulmonary complications in patients who stopped smoking in the perioperative period.<sup>45</sup> Nakagawa et al<sup>46</sup> published a retrospective cohort study of 288 consecutive patients undergoing pulmonary surgery and found that preoperative smoking cessation reduced the risk of pulmonary complications. The authors suggested that cessation should occur at least 4 weeks prior to surgery to lower the risk.<sup>46</sup> Two additional case series were identified that appeared to confirm this relationship. Although there was some discordance on the impact of cessation timing relative to surgery between these two studies, the observed

FIGURE 3. [Section 3.2] Summary of findings: impact of cessation efforts on lung cancer surgical outcomes.

First Author, year	N	% Men	% Pneumonectomy	Postoperative Pulmonary Complication <sup>a</sup> Rate by Smoking Status (%) <sup>b</sup>			
				Current	Recent	Past	Never
Mason 2009 <sup>44</sup>	7,990	48	7	7	6	6	3
Barrera 2005 <sup>45</sup>	300	48	5	23	23	19	8
Nakagawa 2001 <sup>46</sup>	280	58	4	43	54	35	24
Vaporciyan 2002 <sup>47</sup>	261	70	100	-	22	9	15
Groth 2009 <sup>48</sup>	120	100	10	44	19	42	-

<sup>a</sup>Definition of postoperative respiratory complication: *Nakagawa et al*<sup>46</sup>: atelectasis prompting bronchoscopy, pneumonia, PaCO<sub>2</sub> > 50 mm Hg at 24 h after the surgery, air leak or effusion requiring intercostal tube drainage for > 7 d, bronchopleural fistula, empyema, chylothorax, hemothorax requiring drainage or reoperation, tension pneumothorax, pulmonary embolism, lobar gangrene, mechanical ventilation > 72 h, intercostal tube drainage > 14 d for any reason, required FIO<sub>2</sub> > 0.6 or alveolar-arterial gradient > 300 mm Hg 24 h postoperatively. *Vaporciyan et al*<sup>47</sup>: pneumonia or ARDS. *Barrera et al*<sup>45</sup>: respiratory failure requiring ICU admission and/or intubation, pneumonia, atelectasis requiring bronchoscopy, pulmonary embolism, supplemental oxygen at discharge. *Mason et al*<sup>44</sup>: prolonged ventilation (> 48 h postoperatively), need for reintubation, atelectasis requiring bronchoscopy, tracheostomy, pneumonia, or ARDS. *Groth et al*<sup>48</sup>: prolonged air leak (> 7 d), pneumonia, need for reintubation, atrial and ventricular arrhythmias, acute myocardial infarction, stroke, and reoperation.

<sup>b</sup>The definition of smoking status varied widely by study: *Nakagawa et al*<sup>46</sup>: current = smoked within 2 wk of surgery; recent = smoked between 2-4 wk of surgery; past = smoked > 4 wk before surgery. *Vaporciyan et al*<sup>47</sup> and *Groth et al*<sup>48</sup>: recent = smoked < 1 mo before surgery; past = smoked > 1 mo before surgery. *Barrera et al*<sup>45</sup>: recent = smoked within 2 mo of surgery; past = smoked > 2 mo before surgery. *Mason et al*<sup>44</sup>: recent = smoked between 14 d to 1 mo before surgery; past = smoked 1-12 mo before surgery or smoked > 12 mo before surgery (data for this combined group calculated from original data).



differences were believed likely secondary to design issues, including the potential for significant confounding.<sup>47,48</sup> It is important to note that although there may be some indication in these reports that the risk reduction associated with cessation may begin accruing after several weeks of abstinence, the converse conclusion is not warranted. The limitations of this evidence base make it impossible to estimate the relative impact of prioritizing abstinence over the myriad practicalities of procedure scheduling. The data do not support delaying lung cancer surgery to pursue smoking cessation prior to resection.

If patients undergoing surgery for lung cancer represent a group motivated to quit smoking, the perioperative period may represent an opportunity to deliver effective cessation interventions. Guidance on best approaches to this group is available from a relatively small number of studies. Studies evaluating counseling alone in the perioperative period include a heterogeneous group of studies that vary significantly in the specific counseling intervention delivered (Fig 4, Table S5).<sup>49-54</sup> In general, counseling interventions evaluated were straightforward and consisted of face-to-face or telephone counseling, written materials regarding the benefits of quitting, or letters about the risks of smoking in relation to surgery. These studies also varied by population studied and in the timing of the intervention. The majority of these studies did not demonstrate significantly increased short-term cessation rates. For example, Stanislaw and Wewers<sup>49</sup> reported the results of a randomized, controlled trial of patients with cancer admitted to the surgical ward with an anticipated length of stay of at least 3 days. All subjects were current smokers, using at least 10 cigarettes per day, and were assigned to receive either active or “usual care” interventions. In the active group, nurses delivered a counseling intervention during the postoperative period, consisting of three consecu-

tive daily visits and five post-discharge phone visits. Biochemically verified smoking status was assessed 5 weeks after discharge. Compared with the usual care group, patients assigned to the active intervention were 75% more likely to be abstinent at week 5 (75% vs 43%). This difference unfortunately failed to reach statistical significance because of small sample size ( $P < .10$ ). The Ohio State University group also published several small case series which, in aggregate, help give a picture of what can be accomplished in this setting. Patients received nurse-delivered face-to-face and phone counseling derived from the US Public Health Service “5A” approach. A large majority of patients reported at least one quit attempt during the 6-week postoperative period and an intention to quit in the future. Forty percent of patients achieved biochemically confirmed 7-day point prevalence abstinence at follow-up.<sup>52,54</sup> A much larger series was reported by Dresler et al<sup>53</sup> describing the outcomes of physician advice to quit among patients who underwent thoracotomy for resection of lung carcinoma. In the absence of comparator groups, the authors could only conclude that although many patients quit smoking prior to their presentation to a thoracic surgeon, a significant proportion of those who remain smokers can be encouraged to quit by their physician.

Although a broad literature exists guiding behavioral and pharmacologic interventions in general surgical populations, there is a relative paucity of data guiding medication choices in patients with malignancy. To the extent that cancer patient populations overlap with other surgical patient populations, significantly increased smoking cessation should be expected at the time of surgery. Both intensive and brief interventions significantly increase smoking cessation at the time of surgery (relative ratio [RR], 10.76 [95% CI, 4.55-25.46] and RR, 1.41 [95% CI,

FIGURE 4. [Section 3.2] Summary of findings: impact of counseling interventions on smoking cessation rates.

First Author Year	Study Design	Patient Population	Intervention	Abstinence (%)		
				Control	Intervention	p
Stanislaw 1994 <sup>49</sup>	RCT	Cancer pts, having surgery	3 RN in-pt visits, 5 out-pt phone visits	43	75	<0.1
Wewers 1994 <sup>50</sup>	RCT	Postop smokers, multiple diagnoses	3 structured in-pt sessions, 5 weekly out-pt phone sessions	26	38 <sup>a</sup>	<0.1
Griebel 1998 <sup>51</sup>	RCT	Cancer pts having surgery	20 min in-pt session, 5 weekly out-pt phone sessions	14	21	<0.05
Browning 2000 <sup>52</sup>	Quasi-exp case series	Lung Cancer pts having surgery	Intensive(5A) RN program	55	71	0.4
Dresler 1996 <sup>53</sup>	Case series	Lung Cancer pts having surgery	Physician advice to quit	Of quitters, 16% relapsed; rate ↓ with ↑interval post-op		
Wewers 1997 <sup>54</sup>	Case series	Suspected Lung Cancer, preoperative	RN in-pt counseling, 1 out-pt visit after 6 wks	93% ≥1 quit attempt at the 6 wks. 40% confirmed abstinence at 6 wks		

Exp, experimental; post-op, post operatively; pt, patients; RCT = randomized controlled trial; RN = registered nurse; wks, weeks.

<sup>a</sup>For cardiovascular diseases, 40%; cancer, 64%; general surgery diseases, 13%.

1.22-1.63], respectively), and intensive interventions should be expected to retain a significant long-term effect on abstinence rates (RR, 2.96; 95% CI, 1.57-5.55).<sup>43</sup> Our search strategy returned four studies that specifically evaluated the use of pharmacologic therapy among patients with cancer in the perioperative setting (Fig 5, Table S6).<sup>55-58</sup> Only two identified studies were performed in patients with lung cancer. To overcome this limitation, we also retained two studies performed in patients with breast cancer. The study by Park et al<sup>56</sup> used a nonrandomized design to assign 49 smokers with suspected thoracic malignancy to either a control group or a 12-week program consisting of varenicline and smoking cessation counseling. Cotinine-confirmed 7-day point prevalence abstinence rates were 28.1% in the intervention group vs 14.3% in the control group at 2 weeks, and 34.4% vs 14.3%, respectively, at 12 weeks.<sup>56</sup> Although these differences were not statistically significant in this small pilot study, these data suggest that a successful cessation intervention using varenicline can be delivered around the time of diagnosis and prior to therapy. In another case series, Kozower et al<sup>57</sup> described quit rates following a 10-min office-based intervention with a thoracic surgeon. The 40 study participants were offered medication and instructed on use of a state-based quit line, used by 50% and 7.5% of the participants, respectively. Biochemically confirmed abstinence rates at 3-month follow-up were 35% in this group, suggesting that the thoracic surgical environment is a powerful place for effecting abstinence. The breast cancer studies by Thomsen et al<sup>55,58</sup> were also included, given that the social, psychologic, and biologic influences on tobacco outcomes were likely to be sufficiently similar as to provide meaningful insight into the lung cancer population. In a randomized trial, 120 women with breast cancer were randomized to receive either routine preoperative instructions or a 45- to 90-min counseling session 1 week before surgery, along with free NRT.<sup>55,58</sup> Abstinence rates at the time of surgery were 28% in the active intervention group vs 11% for control subjects (RR, 2.49; 95% CI, 1.10-5.60). However, as expected, this low-intensity intervention failed to sustain abstinence for a full year following surgery. At 12-month follow-up, 13% of the intervention group and 9% of the control group remained smoke-free (RR, 1.48; 95% CI, 0.50-4.38). Although these long-range abstinence data are disappointing, they are consistent with observations in the general population in which abstinence is more likely to be maintained through longitudinal, more intensive interventions.

### 3.2.1 Recommendations

#### 3.2.1.1. Among lung cancer patients undergoing surgery, we recommend perioperative cessation

**pharmacotherapy as a method for improving abstinence rates (Grade 1B).**

**3.2.1.2. Among lung cancer patients undergoing surgery for whom pharmacotherapeutic support is either contraindicated or refused, we suggest cessation counseling alone during the perioperative period (Grade 2C).**

**3.2.1.3. Among lung cancer patients undergoing surgery, the timing of cessation does not appear to increase the risk of post-operative complications; we suggest that cessation interventions be initiated in the pre-operative period (Grade 2C).**

*Remark:* Small observed effect sizes and limitations in experimental design do not justify delaying surgical procedures in favor of longer abstinence duration.

**3.2.1.4. For lung cancer patients attempting cessation in conjunction with surgical interventions, we recommend initiating counseling and pharmacotherapy at the outset of surgical intervention (Grade 1B).**

*Remark:* There is substantial evidence suggesting that reliance on short, low intensity cessation interventions such as advice to quit does not improve abstinence outcomes.

### 3.3 What Is the Best Approach to Smoking Cessation Among Patients With Lung Cancer Undergoing Chemoradiotherapy?

The practical realities of chemoradiation treatment can complicate the clinical approach to cessation. Evidence guiding the decisions on counseling approaches during this unique time is presented in Figure 6 and Table S7.<sup>59-62</sup> We identified four studies that dealt specifically with cessation among patient populations with either pulmonary or head/neck (upper airway) malignancies. Schnoll et al<sup>60</sup> conducted a randomized clinical trial based on the Cognitive-Social Health Information-Processing (C-SHIP) model in which they compared cognitive behavioral treatment (CBT) to general health education among 109 patients with cancer. In this study, the investigators found that individually tailored CBT was no more effective at promoting cessation than the more traditional general health information approach to counseling. However, it is important to note that a difference in effect may not have been identified in part because both arms were actively counseled, and both experienced robust abstinence rates. Self-reported abstinence rates at 3-month follow-up were 43.2% in the C-SHIP group and 39.2% among the general health education group ( $P = .83$ ). Gritz et al<sup>62</sup> conducted a trial in which patients with upper aerodigestive tract

FIGURE 5. [Section 3.2] Summary of findings: impact of medication-based interventions on smoking cessation rates.

First Author, year	Study Design	Patient Population	Interventions	Abstinence (%)		
				When (mo)	Control	Inter-vention
Thomsen 2010 <sup>55</sup>	RCT	Breast cancer, preoperative	One 45-90 min counseling session preop, free NRT	12	9	13
Park 2011 <sup>56</sup>	Non-RCT, pre-post design	Suspected thoracic cancer, M0	12 weeks varenicline, 7 weekly counseling sessions	Periop	11	28
Kozower 2010 <sup>57</sup>	Case series	General thoracic surgery	10 min counseling session, free NRT, written materials, quitline referral.	4	14	28
Thomsen 2009 <sup>58</sup>	Qualitative analysis	New breast cancer	One 45-90 min counseling session preop, free NRT.	3		35 <sup>e</sup>
				Four themes emerged: 1) Reflecting upon smoking & health, 2) Escaping social stigma of being a smoker, 3) Heightened awareness of being addicted to smoking, and 4) Enacting a duty of responsibility		

M0 = no distant metastases; mo = months; NS = not significant; preop = preoperative. See Figure 1 and 4 legends for expansion of other abbreviations.

<sup>e</sup>eCO confirmed abstinence at 3 mo = 35%. Outcomes associated with malignant disease, absence of household smoker, but not with use of NRT.

FIGURE 6. [Section 3.3] Summary of findings: impact of counseling interventions on smoking cessation rates.

First Author, year	Study Design	Patient Population	Study Arms		Abstinence (%)		
			Control	Intervention	When	Control	Inter-vention
Wakefield 2004 <sup>59</sup>	RCT	Cancer diagnosis	Brief advice + written material	Motivational Interviewing, phone plus in-person counseling, NRT		11	19
				<i>Quit attempts</i>		62	86
Schnoll 2005 <sup>60</sup>	RCT	H&N cancer, active smoking within 1 mo.	standard general information about cessation	Counseling with Cognitive-Social Health Information-Processing model	1 mo	47	45
					3 mo	39	43
de Bruin-Visser 2012 <sup>61</sup>	Case series	H&N or Lung cancer, active smoker	-	Counseling using Bandura's self-efficacy and Prochaska's stage of change model.	6 mo	-	40
					12 mo	-	33
Gritz 1993 <sup>62</sup>	RCT	H&N cancer. smoking within prior year	Strong advice + written material	7 counseling visits, target quit date, quit contract.	12 mo	77	64
							0.05

H&N = head and neck. See Figure 1, 4 and 5 legends for expansion of other abbreviations.

FIGURE 7. [Section 3.3] Summary of findings: impact of medication-based interventions on smoking cessation.

First Author year	Study Design	Patient Population	Study Arms		Abstinence (%)		
			Control	Intervention	When	Control	Inter-vention
Duffy 2006 <sup>63</sup>	RCT	H&N cancer; screen + for smoking, alcohol abuse, depression	45-min RN assessment	45-min RN assessment; CBT workbook, 9-11 CBT phone sessions, pharmacologic management	6 mo	31	47
Schnoll 2003 <sup>64</sup>	RCT	cancer of any type <sup>a</sup>	Brief advice + Quitline referral	MD counseling based on 5As + NRT + Self help materials + Quitline and/or smoking cessation program referral.	6 mo	12	14
					12 mo	14	13
Schnoll 2010 <sup>65</sup>	RCT	cancer of any type	Counseling x5, NRT x8 wks; placebo.	Counseling x5, NRT x8 wks; bupropion	3 mo	29	31
					7 mo	20	20
Cox 2002 <sup>66</sup>	Matched case-control	lung cancer vs non-lung cancer (chart review)	smoking cessation counseling, pharmacotherapy support		6 mo	14 <sup>b</sup>	22 <sup>c</sup>
Garces 2004 <sup>67</sup>	Matched case-control	H&N cancer vs non-cancer	smoking cessation counseling, pharmacotherapy support		6 mo	26 <sup>b</sup>	33 <sup>d</sup>
							NS

CBT = cognitive behavioral therapy; MD = physician. See Figures 1, 4 and 5 legends for expansion of other abbreviations

<sup>a</sup>Stage I-II cancer of any type; stage III-IV breast, prostate, testicular cancer or lymphoma; performance status 0,1.

<sup>b</sup>Matched patients without cancer.

<sup>c</sup>Patients with lung cancer.

<sup>d</sup>Patients with head and neck cancer.



carcinomas were randomized to receive either standard, one-time advice to quit or an enhanced advice-to-quit session followed by six booster sessions over 6 months. Subjects in both treatment arms had very high rates of continuous abstinence from tobacco at 12 months. Interestingly, abstinence rates were 63.8% in the intervention group and 76.8% in the control group. This difference failed to reach statistical significance. One explanation for these striking observations may be related to design: the experimental intervention may have contaminated the control group, since the same providers were responsible for delivering both forms of advice. In 2004, Wakefield et al<sup>59</sup> reported the results of a randomized clinical trial in which patients with cancer were randomized to either a standard care arm or a motivational interviewing arm. The intervention group received telephone and in-person counseling using motivational interviewing techniques. In addition, NRT was offered to participants who used > 15 cigarettes daily at baseline. The control group received only brief advice to quit plus written educational materials. Quit attempts were made by 86% of the intervention group, compared with 62% of the control subjects ( $P = .01$ ). Differences in biochemically confirmed abstinence at 3 months' follow-up failed to reach statistical significance but suggested a clinically meaningful effect (intervention, 19% vs control, 11%;  $P = .24$ ).

Figure 7 summarizes the studies recovered evaluating medication-based interventions specific to patients diagnosed with cancer (see also Table S8).<sup>63-67</sup> Two of the recovered studies were retrospective chart reviews of hundreds of patients who underwent intensive nicotine dependence treatment, including aggressive CBT and pharmacotherapy support, following a diagnosis of lung or head and neck cancer.<sup>66,67</sup> These studies suggested that treatment including both pharmacotherapy and counseling is effective for patients with cancer. Sanderson Cox et al<sup>66</sup> reported 6-month abstinence rates among lung cancer cases significantly higher than treatment-matched control subjects: 22% vs 14%, respectively (OR, 1.89; 95% CI, 1.09-3.30;  $P = .024$ ). Interestingly, Garces et al<sup>67</sup> noted that 6-month abstinence rates were highly correlated to the amount of elapsed time between cancer diagnosis and tobacco use treatment. Patients who were treated within 3 months of their diagnosis were more than twice as likely to achieve abstinence compared with those who waited longer (47% vs 22%,  $P = .021$ ). Although the retrospective design of these studies may limit their generalizability to other treatment settings, their findings nonetheless provide a compelling rationale for integrating intensive cessation pharmacotherapy into treatment plans beginning soon after the diagnosis of cancer. Three randomized

clinical trials were also recovered. Schnoll et al<sup>64</sup> conducted a clinical trial in which patients with cancer were randomized to either usual care or a physician-based tobacco intervention that included both advice to quit for all patients and pharmacotherapy for some patients. No statistically significant differences in quit rates were found at the 6- and 12-month follow-ups, but this finding may have been affected by the fact that treatment providers gave both the experimental and control treatments, potentially contaminating the control condition. Duffy et al<sup>63</sup> conducted a multisite clinical trial in which patients with cancer were randomized to either usual care or a nurse-delivered experimental intervention of cognitive behavioral treatment and medication management. A significant treatment effect was observed at 6-month follow-up (47% quit in experimental arm vs 31% in treatment as usual arm). Schnoll et al<sup>65</sup> conducted a double-blind randomized clinical trial comparing SR bupropion 300 mg to matching placebo. All patients were stratified by depressive symptom scores. A main effect of bupropion was not found; however, in patients with cancer with depressive symptoms, bupropion appeared to improve abstinence rates and improve QOL compared with patients with depressive symptoms treated with placebo. Overall, however, patients with cancer with depressive symptoms displayed lower rates of quitting smoking compared with those without depressive symptoms.

### 3.3.1 Recommendations

**3.3.1.1. Among lung cancer patients undergoing chemotherapy, we recommend cessation interventions that include counseling and pharmacotherapy to improve abstinence rates (Grade 1B).**

**3.3.1.2. Among lung cancer patients with depressive symptoms, we suggest cessation pharmacotherapy with bupropion as a method to improve abstinence rates, depressive symptoms, and QOL (Grade 2B).**

**3.3.1.3. Among lung cancer patients for whom pharmacotherapeutic support is either contraindicated or refused, we suggest cessation counseling alone as a method to improve abstinence rates (Grade 2C).**

### 3.4 What Is the Impact of Smoking Cessation on Patients With Lung Cancer Undergoing RT?

Because RT warrants significant attention to healing and prevention of complications, an understanding of the impact of cessation, and cessation pharmacotherapy, on the outcomes of RT is also warranted. Table S9<sup>68,69</sup> summarizes the two studies recovered that directly address this question. Zevallos et al<sup>68</sup>

conducted a retrospective review that showed that continued smoking appeared to increase risk of complications from RT. In this prospective cohort study, 81 patients with head/neck cancer undergoing RT were treated with combination counseling and pharmacotherapy. In this population, 37 abstainers and 44 nonabstainers were identified. Hospitalization during RT was experienced by 34% of nonabstainers but only 14% of abstainers (OR, 1.3; 95% CI, 1.02-1.68;  $P = .03$ ). Osteoradionecrosis rates were also substantially affected by tobacco dependence treatment. Nonabstainers experienced this complication at much higher rates than their abstaining counterparts: 21% vs 3%, respectively (OR, 1.2; 95% CI, 1.04-1.43;  $P = .02$ ). In another retrospective review, Semrau et al<sup>69</sup> performed a multivariate regression that showed no effect of smoking on survival. Unfortunately, the classification method made no distinction between past and current smoking. As a consequence, only 4% of their population was classified as never smokers for the analysis. No comparisons could be made to estimate the impact of the tobacco variable on survival in this data set.

### 3.4.1 Recommendation

**3.4.1.1. Among lung cancer patients undergoing radiotherapy, we recommend cessation interventions that include counseling and pharmacotherapy (Grade 1C).**

## 4.0 DISCUSSION

Recommendations in this article were designed to balance the urgent need for tobacco use treatment in patients with cancer against the realities of oncologic practice. Passive approaches, such as the distribution of self-help materials and reliance on screening protocols or diagnostic testing to create motivation to quit, are not supported by the evidence. In general, the evidence supports active cessation interventions in this group, including tailored pharmacotherapy in all patients who can tolerate it. An analysis of the incremental cost-effectiveness of smoking cessation prior to lung cancer surgical resection suggests that even intensive interventions are cost-effective at both 1- and 5-year end points.<sup>70</sup>

Unfortunately, the evidence specifically guiding tobacco dependence treatment of patients with cancer does not yet accurately reflect the importance of the clinical questions and the special issues most relevant to these patients. The paucity of well-designed studies leaves significant gaps in our understanding of best approaches to treating this particularly vulnerable group. It is important that future research continue to shed light on the specific issues facing this

population and that study designs be used with standardized definitions and outcome measures.<sup>71</sup> Examples of important clinical research questions yet to be answered include:

- What are the best strategies for effecting cessation in the relatively time-constrained circumstance of the preoperative period?
- Given the typical symptoms associated with nicotine withdrawal, which combination pharmacotherapy strategies are best tolerated among patients undergoing chemotherapy? How do we best control withdrawal symptoms during periods of forced abstinence, including with patients unwilling to quit?
- What is the most effective/best tolerated dose range for first-line pharmacotherapeutic agents in this population? How do we best manage continued abstinence in the face of complex medication regimens, anorexia, or other realities of ongoing cancer care?
- How do we best manage relapse to smoking after lung cancer cure?
- Are there any significant clinical interactions between cessation pharmacotherapeutic agents and chemotherapy? Does choice of cessation drug affect chemoradiation side effect incidence or cancer outcome?

In summary, tobacco dependence is common in oncologic practice. Perhaps because of the dramatic nature of the consequences of tobacco use, dependence behaviors among patients with cancer are particularly frustrating and often poorly understood. The insidious effect of this paradox is to foster a sense of culpability among patients and therapeutic nihilism among clinicians. The care of patients with lung cancer is improved when tobacco dependence is addressed. An overwhelming wealth of evidence supports the effectiveness, benefit, and fiscal sensibility of tobacco dependence treatment in general populations of smokers. Excellent resources are available to help clinicians be more efficient in the pursuit of this important therapeutic goal.

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