

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Smoking Cessation

Version 1.2018 — June 18, 2018

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NCCN Guidelines Version 1.2018 Smoking Cessation

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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial.

Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical_trials/physician.html](#).

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

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NCCN Guidelines Version 1.2018

Smoking Cessation

Updates in Version 1.2018 of the NCCN Guidelines for Smoking Cessation from Version 2.2017 include:

INTRO

- Last bullet revised: "Smoking cessation should be offered as part of oncology treatment and continued throughout the entire oncology care continuum, *including surgery and during end-of-life care.*"
- Footnote "a" revised: "Combination NRT = Nicotine patch + short-acting NRT (ie, lozenge, gum, inhaler), ~~nasal spray~~ for cravings."

SC-1

- Separated pathways for long-term former smokers and those who have never smoked.
- Recommendation revised for long-term former smokers/those who never smoked: "Encourage patient to remain smoke-free *and not use any combustible products.*"
- Footnote "b" revised: "... encouraged to discontinue the use of all combustible products (eg, cigars, hookah) ~~; marijuana~~ and smokeless tobacco products."

SC-2

- Under nicotine dependency, revised the second sub-bullet: "How soon do you smoke after you wake up in the morning? (*ie, within 5 minutes. See Discussion*)"
- Last bullet added: "Smoking status of individuals within household"
- Clarified which pathway applies to recent quitters: "Ready to quit within 4 weeks *or has quit within prior 30 days*"
- Under management, revised the first sub-bullet: "Establish personalized quit plan based on *evaluation nicotine dependency and prior quit attempts.*"

SC-3

- Under evaluation:
 - ▶ Added the following risk factor: "Current or prior history of mental illness."
 - ▶ In last bullet, changed "narcotics" to "opioids."
 - ▶ After management for those with ≥ 1 risk factor for relapse, timing of reevaluation revised: "...~~regularly~~ *at each visit or more often as indicated.*"
- Footnote "m" revised: "Providers should discuss risk of relapse and smoking slips and provide guidance and support to encourage continued smoking cessation attempts. *The benefits of using NRT in a former smoker can be weighed against the risk of relapse to combustible cigarette smoking, for which there is no safe level.*"

SC-3 (continued)

- Footnote removed: "When considering pharmacotherapy maintenance options for patients who have been nicotine free for an extended period of time (eg, 30 days or longer), carefully consider the potential effects of re-introducing nicotine through NRT or advocating for the use of combination NRT."

SC-4

- The following primary pharmacotherapies were changed from category 2A to category 1 recommendations:
 - ▶ Combination NRT + behavior therapy x 12 wk (category 1)
 - ▶ Varenicline + behavior therapy x 12 wk (category 1)
- Added the following to the primary therapy options: "(For standard dose, see SC-F, 2 of 2)" (Also on SC-5)
- Revised first bullet under assessment/follow-up: "Within 3 wk after ~~cessation therapy begins~~ *cessation therapy begins (within 1 wk preferred)*"
- After determining the patient is smoke-free, second bullet revised: "Extend duration of pharmacotherapy as clinically indicated (*ie, 6mo or longer*)"
- Footnote "u" added: "Patient assistance programs may be available."
- Footnote "w" revised: "Nicotine withdrawal symptoms typically peak within 4–2 weeks of quitting. ~~Patients who do not quit immediately may quit at some later point after withdrawal symptoms subside; therefore,~~ Encourage continued therapy through brief slips."
- Footnote "y" added: "Varenicline can be used up to 1 year for continued abstinence."
- Footnote removed: "Varenicline should be avoided for patients with brain metastases due to seizure risk."

SC-5

- Footnote "z" revised: "Decision to *continue or switch* therapy should be based on *prior cessation success, patient preference, toxicity, and/or a change in clinical status (eg, upcoming surgery).*"

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[Continued](#)



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Smoking Cessation

Updates in Version 1.2018 of the NCCN Guidelines for Smoking Cessation from Version 2.2017 include:

SC-B

- Under treatment-specific risks, added the following to the second bullet: "Patients who receive RT and continue to smoke may also have an increased risk of developing second primary cancer."
- References added:
 - ▶ Kaufman EL, Jacobson JS, Hershman DL, et al. Effect of breast cancer radiotherapy and cigarette smoking on risk of second primary lung cancer. *J Clin Oncol* 2008; 26(3):392-398.
 - ▶ Arnold M, Liu L, Kenter GG, et al. Second primary cancers in survivors of cervical cancer in The Netherlands: Implications for prevention and surveillance. *Radiother Oncol* 2014;111(3):374-381.
 - ▶ Tucker MA, Murray N, Shaw EG, et al. Second primary cancers related to smoking and treatment of small-cell lung cancer. *Lung Cancer Working Cadre. J Natl Cancer Inst* 1997;89(23):1782-1788.
 - ▶ Neugut AI, Murray T, Santos J, et al. Increased risk of lung cancer after breast cancer radiation therapy in cigarette smokers. *Cancer* 1994; 73(6): 1615-1620.

SC-C

- Resources for patients:
 - ▶ Added: American Society for Clinical Oncology (ASCO)- Stopping Tobacco Use After a Cancer Diagnosis
 - ▶ Combined entries and made modifications for the National Cancer Institute and Smokefree.gov
 - ▶ Added resource from the American Lung Association, Freedom from smoking.
 - ▶ Combined entries for TRICARE and UCANQUIT2.
- Resources for Health Professionals
 - ▶ Added ASCO Resource- Tobacco Cessation Guide for Oncology Providers
 - ▶ Added: National Behavioral Health Network

SC-D

- Surgery recommendations have been significantly revised and reorganized.

SC-E (1 of 2)

- Fourth bullet revised: "In smokers with cancer, there is a high incidence of depression, anxiety, and stress, all of which are common causes of relapse. *Providers should routinely assess for these symptoms among smokers throughout treatment for tobacco dependence. It may be optimal...*"

SC-E (2 of 2)

- First bullet revised: "Four or more sessions during each 12-week course of pharmacotherapy. The first session is recommended within ~~the first 2-3 weeks of cessation~~ (*within 1 week preferred*)."

SC-F (1 of 2)

- First preferred primary therapy option revised: "Combination NRT: Nicotine patch + short-acting NRT ~~for cravings~~ (lozenge/gum/ inhaler/~~nasal spray~~)"
- Bupropion has been changed from a category 2B to a category 2A subsequent therapy option.
- Footnote "b" revised: "~~Varenicline and~~ Bupropion should be avoided for patients with brain metastases due to seizure risk. *Varenicline should be used with caution for those with seizure risk.*"

SC-F (2 of 2)

- Combination NRT dose, last bullet revised: "Short-acting NRT every 2 hr (while awake), or more often as needed, ~~every 1-2 hours for cravings~~"
- Varenicline
 - ▶ Dose, last bullet revised: "~~Week 2-12~~ *Day 8 to end of treatment: 1 mg orally, twice daily, if tolerated*"
 - ▶ Adverse Effects/contraindications revised based on the updated package insert: Removed "See Manufacturer Black Box Warning, and weigh the substantial benefits of immediate smoking cessation versus risks of increased hostility, depression, or suicidal behavior" and "Contraindicated for patients with brain metastases due to seizure risk" and added "*Use with caution for patients with seizure risk.*"

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

GENERAL PRINCIPLES OF THE SMOKING CESSATION GUIDELINES

These guidelines are focused on smoking cessation recommendations for patients with cancer. There are health benefits to smoking cessation even after a cancer diagnosis, regardless of stage or prognosis, namely improvement in cancer treatment outcomes, primary cancer recurrence, and secondary cancers. It is never too late for patients with cancer to stop smoking cigarettes and experience health benefits. Smoking and nicotine addiction is a chronic relapsing disorder. Smokers with cancer often demonstrate high-level nicotine dependence. The NCCN Panel recommends that treatment plans for all smokers with cancer include the following:

- Evidence-based motivational strategies and behavior therapy,
- Evidence-based pharmacotherapy, and
- Close follow-up with retreatment as needed.

Clinical Recommendations:

- **Combining pharmacologic therapy and behavior therapy is the most effective approach and leads to the best results for smoking cessation.**
 - ▶ The two most effective pharmacotherapy agents are combination nicotine replacement therapy^a (NRT) and varenicline.
 - ▶ High-intensity behavior therapy with multiple counseling sessions is most effective, but at least a minimum of brief counseling is highly recommended. Quitlines may be used as an adjunct, especially in lower-resource settings.
- **Smoking status should be documented in the patient health record. Patient health records should be updated at regular intervals to indicate changes in smoking status, quit attempts made, and interventions utilized.**
- **Smoking relapse and brief slips are common and can be managed. Providers should discuss this and provide guidance and support to encourage continued smoking cessation attempts. Smoking slips are not necessarily an indication to try an alternative method. It may take more than one quit attempt with the same therapy to achieve long-term cessation.**
- **Smoking cessation should be offered as an integral part of oncology treatment and continued throughout the entire oncology care continuum, including surgery and end-of-life care. An emphasis should be put on patient preferences and values when considering the best approach to fostering smoking cessation during end-of-life care.**

^aCombination NRT = Nicotine patch + short-acting NRT (ie, lozenge, gum, inhaler).

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EVALUATION AND ASSESSMENT OF PATIENT SMOKING^b

INITIAL EVALUATION^c

STATUS

Assess current cigarette smoking status of all patients with cancer:^{c,d,e}

- Have you ever smoked cigarettes?
- Do you currently smoke cigarettes or have you smoked in the last 30 days?

Current smoker and/or those who have smoked within the last 30 days

[See Assessment of Current Smokers \(SC-2\)](#)

Former smoker or recently quit (>30 days–1 year since patient last smoked)

[See Assessment of Former Smokers \(SC-3\)](#)

Long-term former smoker (≥1 year since last smoked)

Encourage patient to remain smoke-free and not to use any combustible products^b

Never smoked

^bRecommendations in this guideline apply to cessation of cigarette smoking. Patients with cancer should be encouraged to discontinue the use of all combustible products (eg, cigars, hookah) and smokeless tobacco products. For information about e-cigarettes, [see Principles of Alternative Approaches to Smoking Cessation \(SC-A\)](#).

^cInitial evaluation and assessment of patient smoking may be completed by any member of the health care team, including physicians, nurses, medical assistants, health educators, or other dedicated staff.

^dSmoking status should be documented in the patient health record and assessment should be repeated at every visit (less often for patients with remote smoking histories).

^eSmoking cessation should be offered to all smokers with cancer regardless of cancer prognosis. [See Smoking-Associated Risks for Patients With Cancer \(SC-B\)](#).

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CURRENT SMOKERS AND THOSE WHO HAVE SMOKED WITHIN LAST 30 DAYS

EVALUATION^f

Assess and document in the patient health record:

- **Nicotine dependency:**
 - ▶ How much do you currently smoke per day? What is the typical amount you smoked per day within the last 3 months?
 - ▶ How soon do you smoke after you wake up in the morning? (ie, within 5 minutes. See [Discussion](#))
 - ▶ Do you use any other type(s) of tobacco/nicotine products and if so, how much? (eg, pipes, cigars, snuff, e-cigarettes)
- **History of quit attempts:**
 - ▶ What is the longest period you have gone without smoking?
 - ▶ When was your last quit attempt?
 - ▶ Did you use anything to help you quit in the past? If so, what?
 - ◊ Unaided
 - ◊ Medications^g (eg, varenicline, bupropion, NRT)
 - ◊ Support group
 - ◊ Behavior therapy
 - ◊ Quitlines, websites, smart phone applications, or other media
 - ◊ E-cigarettes^h
 - ◊ Other
 - ▶ Why were previous quit attempts unsuccessful? (eg, side effects, cost, continued cravings, did not work)
- **Patient readiness to quit^{i,j}**
- **Smoking status of individuals within household**

Engage patients in motivational dialog about smoking cessationⁱ

- Review risks of smoking and benefits of quitting ([See SC-B](#))
- Provide patient education resources ([See SC-C](#))

Ready to quit within 4 weeksⁱ or has quit within prior 30 days

Not ready to quit within 4 weeksⁱ

MANAGEMENT

- Establish or reinforce personalized quit plan based on:
 - ▶ Evaluation^k
 - ▶ Smoking cessation therapy options ([see SC-4](#))
- Set quit date as soon as possible.
- Encourage smoking cessation as soon as possible if cancer surgery is planned.^l
- Discuss risk of relapse.^m

- Assess and address barriers and concerns of patient.
- Consider smoking reduction with a goal of setting a quit date in the near future^j
 - ▶ Encourage immediate initiation of pharmacotherapy for targeted reduction of cigarettes per dayⁿ

Begin smoking cessation treatment ([See SC-4](#))

Reassess readiness to quit at each visit

^fFor lung cancer screening recommendations, see [NCCN Guidelines for Lung Cancer Screening](#).

^gDocument type and dose of medications used during previous quit attempts.

^hThere is currently insufficient evidence to support the use of electronic nicotine delivery systems (e-cigarettes) in smoking cessation for patients with cancer.

ⁱPhysicians and members of the health care team should discuss potential benefits of quitting with each patient. Readiness to quit is to be determined by both physician and patient.

^jMaking an immediate quit attempt is recommended but smoking reduction may be considered with a goal of cessation at a future quit date (ie, 1–3 mo).

^kAdjustments to therapy length, intensity, and surveillance may be considered, as clinically indicated, for patients with high nicotine dependency and/or prior unsuccessful quit attempts.

^lLonger periods of smoking cessation confer better surgical outcomes but should not delay appropriate timing of cancer resection. See [Principles of Smoking Cessation and Cancer Surgery \(SC-D\)](#).

^mProviders should discuss risk of relapse and smoking slips and provide guidance and support to encourage continued smoking cessation attempts. Consider potential effects or unintended consequences of reintroducing nicotine. See [Principles of Behavioral Strategies \(SC-E\)](#).

ⁿSee [Principles of Smoking Cessation Pharmacotherapy \(SC-F\)](#).

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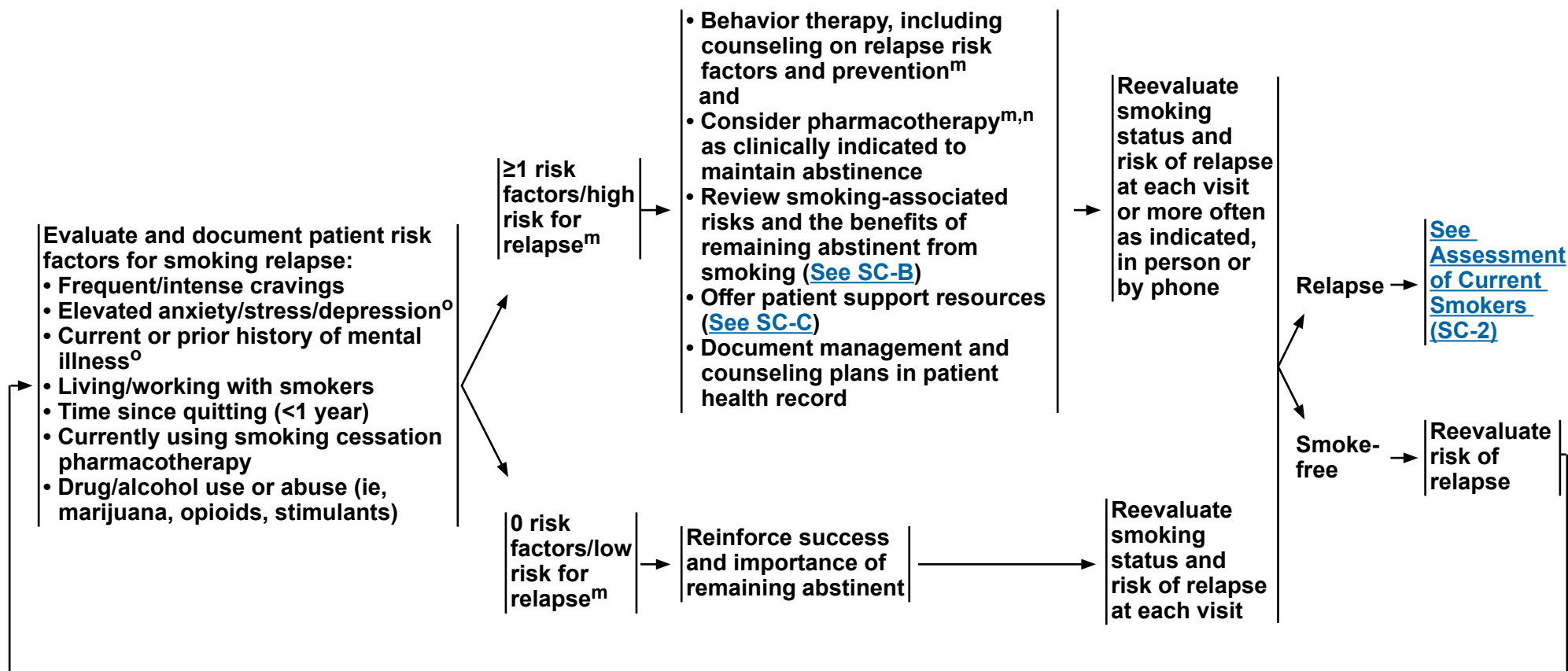
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Smoking Cessation

FORMER SMOKERS AND RECENT QUITTERS (>30 Days Since Last Smoked)

EVALUATION

MANAGEMENT



^mProviders should discuss risk of relapse and smoking slips and provide guidance and support to encourage continued smoking cessation attempts. The benefits of using NRT in a former smoker can be weighed against the risk of relapse to combustible cigarette smoking, for which there is no safe level. [See Principles of Behavioral Strategies \(SC-E\)](#).

ⁿ[See Principles of Smoking Cessation Pharmacotherapy \(SC-F\)](#).

^oRefer to specialist for management of psychiatric comorbidities.

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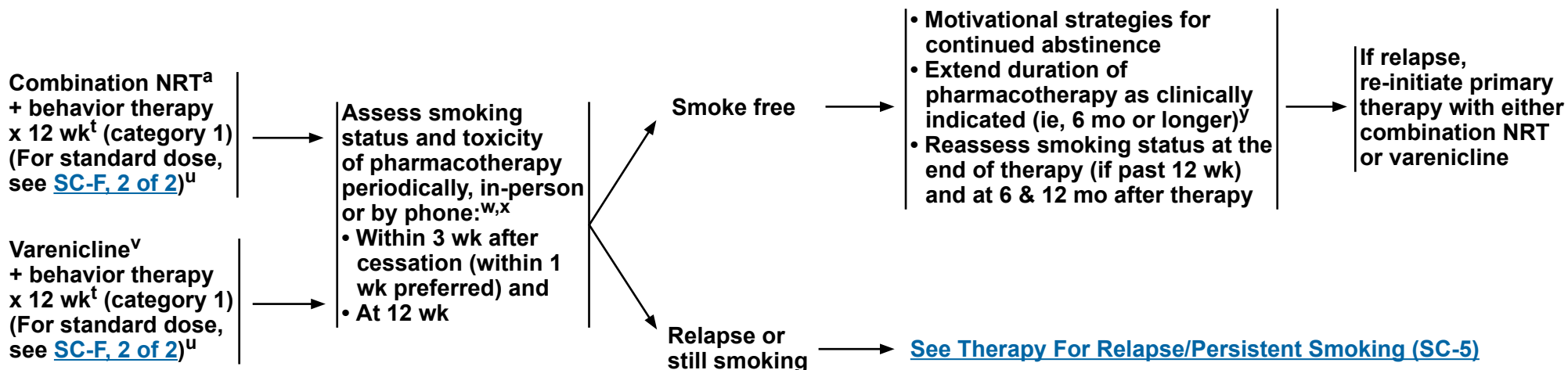


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GENERAL APPROACH TO SMOKING CESSATION FOR PATIENTS WITH CANCER AND SURVIVORS

PRIMARY THERAPY^{n,p,q,r}

ASSESSMENT/FOLLOW-UP



^aCombination NRT = Nicotine patch + short-acting NRT (gum/lozenge/inhaler).

ⁿSee [Principles of Smoking Cessation Pharmacotherapy \(SC-F\)](#).

^pSee [Principles of Behavioral Strategies \(SC-E\)](#).

^qEfficacy data are lacking for the use of e-cigarettes and alternative therapies (eg, hypnosis, acupuncture, nutritional supplements). Use of evidence-based cessation methods should be encouraged to avoid delay in achieving smoking abstinence. See [Principles of Alternative Approaches to Smoking Cessation \(SC-A\)](#).

^rThe use of marijuana, or other substances associated with smoking relapse, is discouraged for those attempting to quit smoking.

^tA minimum of 4 sessions of individual/group therapy in 12 weeks is preferred, but at least brief counseling is required. See [Principles of Behavioral Strategies \(SC-E\)](#).

^uPatient assistance programs may be available.

^vNausea is a common side effect of varenicline and may need to be managed for patients with cancer, especially during chemotherapy.

^wNicotine withdrawal symptoms typically peak within 2 weeks of quitting. Encourage continued therapy through brief slips.

^xAdjust behavior therapy frequency as needed, and adjust pharmacotherapy dose for undesirable side effects or if high risk of relapse is suspected.

^yVarenicline can be used up to 1 year for continued abstinence.

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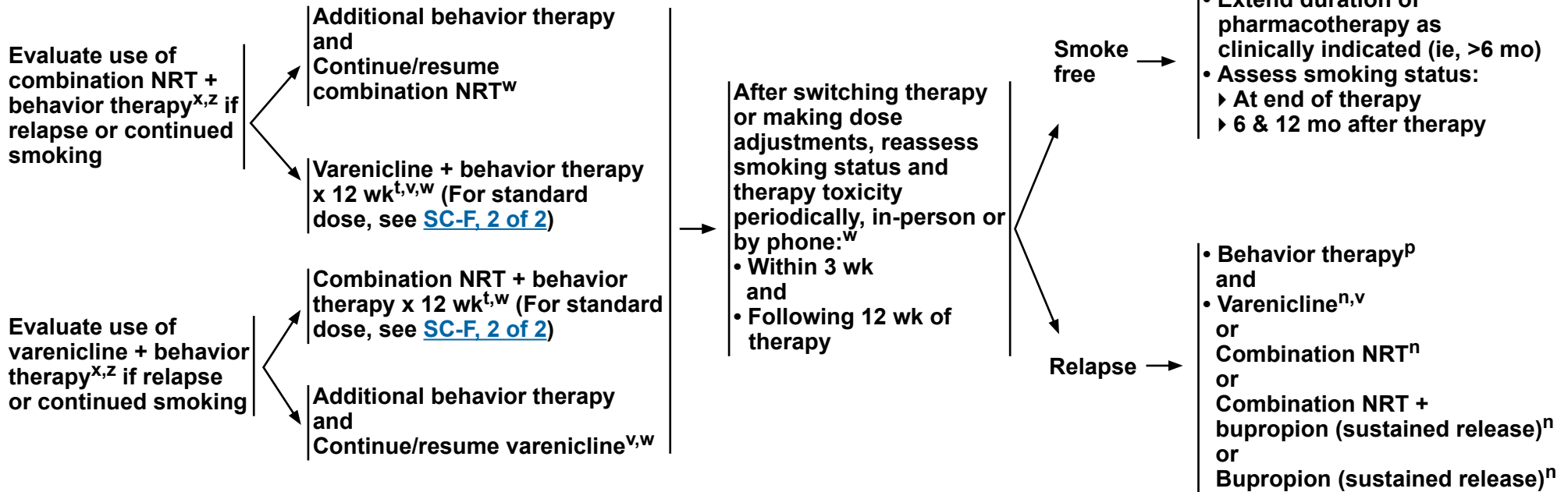


GENERAL APPROACH TO SMOKING CESSATION FOR PATIENTS WITH CANCER AND SURVIVORS

THERAPY FOR RELAPSE/ PERSISTENT SMOKING^{n,p,q,r,z}

ASSESSMENT/FOLLOW-UP

ADDITIONAL THERAPY/ FOLLOW-UP



ⁿSee [Principles of Smoking Cessation Pharmacotherapy \(SC-F\)](#).

^pSee [Principles of Behavioral Strategies \(SC-E\)](#).

^qEfficacy data are lacking for the use of e-cigarettes and alternative therapies (eg, hypnosis, acupuncture, nutritional supplements). Use of evidence-based cessation methods should be encouraged to avoid delay in achieving smoking abstinence. See [Principles of Alternative Approaches to Smoking Cessation \(SC-A\)](#).

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^xAdjust behavior therapy frequency as needed, and adjust pharmacotherapy dose for undesirable side effects or if high risk of relapse is suspected.

^zDecision to continue or switch therapy should be based on prior cessation success, patient preference, toxicity, and/or a change in clinical status (eg, upcoming surgery).

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**PRINCIPLES OF ALTERNATIVE APPROACHES TO SMOKING CESSATION**

- Offer motivational and behavioral support to all patients attempting to quit smoking, regardless of what smoking cessation method(s) is/are being used. [See Principles of Behavioral Strategies \(SC-E\)](#)
- For patients who are unable or unwilling to quit, one potential strategy is smoking reduction with a goal of quitting. [\(See SC-2\)](#)
- Encourage the use of evidence-based cessation methods to avoid delays in achieving abstinence.
- For patients using alternative approaches, including electronic cigarettes, continue to provide support during quit attempts.
- Relapse and smoking slips are common. Remind patients that repeated attempts with evidence-based methods are frequently needed to achieve longer-term abstinence.

Electronic Nicotine Delivery Systems (ENDS) or "E-Cigarettes"

- ENDS are not FDA-approved smoking cessation devices.
- There is currently insufficient evidence to support the use of e-cigarettes in smoking cessation, alone or in combination with evidence-based smoking cessation methods. There is also insufficient evidence regarding the safety and efficacy of e-cigarette use in patients with cancer.
 - ▶ The American Heart Association, American Association for Cancer Research (AACR), and American Society of Clinical Oncology (ASCO) recognize the potential for ENDS to alter existing smoking behaviors, as well as the lack of definitive data regarding associated benefits and harms.^{1,2} However, ENDS are not recommended by these associations because of the insufficient data on efficacy and safety.
 - ▶ According to the US Preventive Services Task Force (USPSTF), “Current evidence is insufficient to recommend electronic nicotine delivery systems (ENDS) for tobacco cessation in adults, including pregnant women. The USPSTF recommends that clinicians direct patients who smoke tobacco to other cessation interventions with established effectiveness and safety.”³

Other Alternative Methods

- There is currently insufficient evidence to support the use of alternative methods (eg, hypnosis, acupuncture, nutritional supplements) when used alone and in combination with standard smoking cessation methods.^{4,5}
- Prior unsuccessful quit attempts with conventional therapies do not justify the use of unproven alternative cessation methods because multiple attempts with evidence-based methods may be necessary to achieve abstinence.
- There are very limited, low-quality data regarding the efficacy of exercise-based interventions.⁶

¹Brandon TH, Goniewicz ML, Hanna NH, et al. Electronic nicotine delivery systems: a policy statement from the American Association for Cancer Research and the American Society of Clinical Oncology. *J Clin Oncol* 2015;33:952-963.

²Bhatnagar A, Whitsel LP, Ribisl KM, et al. Electronic cigarettes: a policy statement from the American Heart Association. *Circulation* 2014;130:1418-1436.

³Final Update Summary: Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavioral and Pharmacotherapy Interventions. U.S.

Preventive Services Task Force. September 2015. <http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions1?ds=1&s=tobacco>

⁴Barnes J, Dong CY, McRobbie H, et al. Hypnotherapy for smoking cessation. *Cochrane Database Syst Rev* 2010:CD001008.

⁵White AR, Rampes H, Liu JP, et al. Acupuncture and related interventions for smoking cessation. *Cochrane Database Syst Rev* 2014;1:CD000009.

⁶Ussher MH, Taylor AH, Faulkner GE. Exercise interventions for smoking cessation. *Cochrane Database Syst Rev* 2014;8:CD002295.

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SMOKING-ASSOCIATED RISKS FOR PATIENTS WITH CANCER

- The 2014 Surgeon General's Report¹ stated that:
 - ▶ Sufficient evidence exists to support a causal relationship between smoking and adverse health outcomes, increased all-cause mortality and cancer-specific mortality, and increased risk for secondary primary cancers.
 - ▶ Existing evidence is suggestive of a link between smoking and increased risk of cancer recurrence, poor treatment response, and increased treatment-related toxicity.
- Providers should:
 - ▶ Inform patients of the potential benefits of smoking cessation, including improved survival, treatment outcomes, and health-related quality of life, as well as decreased treatment-related toxicity, drug side effects, and surgical complications.
 - ▶ Educate patients on the specific risks of smoking during treatment for their particular cancer.
 - ▶ Encourage smoking cessation as far in advance as possible before initiating cancer treatment.
 - ▶ Consider patient smoking status prior to initiating treatment and when making decisions regarding treatment selection, dosage, and timing of initiation.
 - ▶ Discuss smoking cessation with all patients who smoke. Patient satisfaction is enhanced when smoking cessation is offered by providers.
 - ▶ Encourage smoking cessation among all members of the household for the benefit of the patient.

Treatment-Specific Risks (see [Discussion](#) for additional information)

- Smoking can impact the metabolism of chemotherapy and targeted therapy.
 - ▶ Smoking effects on cytochrome P450 enzymes may include altered drug clearance time and plasma concentration, potentially impacting the efficacy of certain drugs. Providers should consider whether patients are at risk for altered drug metabolism due to smoking and determine if medication or dose adjustments may be required. Drugs whose metabolisms are known to be affected include erlotinib, irinotecan, and bendamustine.²⁻⁶
- Smoking increases risk of radiation therapy (RT)-associated treatment complications during RT and may decrease treatment response.⁷⁻⁹ Patients who receive RT and continue to smoke may also have an increased risk of developing second primary cancer.¹⁰⁻¹³
- Smoking is associated with increased rates of postoperative complications and mortality after cancer surgery.
 - ▶ Compared with nonsmokers, patients who smoke may experience decreased health-related quality of life after cancer surgery (eg, dyspnea, fatigue, pain).¹⁴⁻¹⁶
 - ▶ Smoking may impair wound healing following surgery for cancer.^{17,18}
 - ▶ Increased infection rates, cardiovascular and pulmonary complications, and longer postoperative hospital stays are more commonly observed in patients who smoke.¹⁹
 - ▶ Postoperative mortality rates are higher among patients who smoke.²⁰

Potential Nicotine Effects on Cancer and Cardiovascular Risks (see [Discussion](#) for additional information)

- Blood nicotine levels from NRT, including combination NRT, are significantly less than from smoking cigarettes. Therefore, providers and smokers should not be dissuaded from using NRT to foster quitting and long-term cessation.
- There is insufficient evidence that NRT causes cancer in humans.²¹⁻²⁵
- There is insufficient evidence that NRT increases the risk of myocardial infarction or cardiovascular disease.

[References on next page](#)

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SMOKING-ASSOCIATED RISKS FOR PATIENTS WITH CANCER**REFERENCES**

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Smoking Cessation

SMOKING CESSATION RESOURCES FOR PATIENTS AND HEALTH PROVIDERS

CANCER-RELATED RESOURCES FOR PATIENTS^a

Organization	Website/Contact Info	Guides for Quitting/Additional Resources
American Cancer Society (ACS)	<ul style="list-style-type: none"> Website: https://www.cancer.org/healthy/stay-away-from-tobacco.html Phone: 1.800.227.2345 	Guide to quitting smoking: http://www.cancer.org/healthy/stayawayfromtobacco/guidetoquittingsmoking/index
American Lung Association	<ul style="list-style-type: none"> Website: http://www.lung.org/stop-smoking/ Lung Cancer Helpline: 1.844.252.5864 	Freedom from Smoking: http://www.lung.org/stop-smoking/join-freedom-from-smoking/
American Society for Clinical Oncology (ASCO)	https://www.asco.org/practice-guidelines/cancer-care-initiatives/prevention-survivorship/tobacco-cessation-control	Stopping Tobacco Use After a Cancer Diagnosis: https://www.asco.org/sites/new-www.asco.org/files/content-files/practice-and-guidelines/documents/stopping-tobacco-use-booklet.pdf
Smokefree.gov	<ul style="list-style-type: none"> Website: https://www.smokefree.gov/ NCI Quitline: 1.877.448.7848 Springboard Beyond Cancer: https://survivorship.cancer.gov/ LiveHelp: https://livehelp.cancer.gov/ 	<ul style="list-style-type: none"> QuitGuide App: https://smokefree.gov/apps-quitguide SmokeFree Text Messaging Programs (available for adults, teens, moms, veterans, espanol): https://smokefree.gov/smokefree-text-messaging-programs "Clearing the Air: Quit Smoking Today": http://smokefree.gov/sites/default/files/pdf/clearing-the-air-accessible.pdf

GENERAL RESOURCES FOR PATIENTS^a

Organization	Website	Quitline/Online Support
American Heart Association	https://healthyforgood.heart.org/	
American Indian Commercial Tobacco Program	https://americanindian.quitlogix.org	1.855.372.0037
Asian Smokers' Quitline	http://www.asiansmokersquitline.org/	Mandarin/Cantonese: 1.800.838.8917; Korean: 1.800.556.5564; Vietnamese: 1.800.778.8440
Centers for Disease Control and Prevention (CDC) and National Network of Tobacco Cessation Quitlines	https://www.cdc.gov/tobacco/quit_smoking/cessation/pdfs/1800quitnow_faq.pdf	<ul style="list-style-type: none"> English: 1.800.QUIT.NOW (1.800.784.8669) Spanish: 1.855.335.3569
Ex: A New Way To Think About Quitting Smoking	http://www.becomeanex.org/	ExCommunity: https://excommunity.becomeanex.org
TRICARE and UCanQUIT2 (Military and family)	http://www.tricare.mil/HealthWellness/Tobacco.aspx	Text support (SmokefreeMIL): https://tricare.mil/HealthWellness/Tobacco/UCanQuit2/How-to-Quit/SmokeFreeMIL

^aFree or low-cost support is sometimes available for uninsured or underinsured patients. Resources may vary by organization and location. Contact each organization to learn more about the availability of free and low-cost smoking cessation resources offered regionally.

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[Continued](#)



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Smoking Cessation

SMOKING CESSATION RESOURCES FOR PATIENTS AND HEALTH CARE PROVIDERS

CANCER-RELATED RESOURCES FOR HEALTH PROFESSIONALS

Organization	Guidelines and Resources
American Association for Cancer Research (AACR)	Policy Statement: http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/Documents/AACRStatement_TobaccoUseCancerPatients_2013_CCR_f3f578.pdf
American Society of Clinical Oncology (ASCO)	Tobacco Cessation Guide for Oncology Providers: https://www.asco.org/sites/new-www.asco.org/files/content-files/blog-release/documents/tobacco-cessation-guide.pdf
NCCN Guidelines for Lung Cancer Screening	http://www.nccn.org/professionals/physician_gls/pdf/lung_screening.pdf
NCCN Guidelines for Survivorship	http://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf
NCI- Physician Data Query (PDQ)	https://www.cancer.gov/about-cancer/causes-prevention/risk/tobacco/quit-smoking-hp-pdq
U.S. Department of Health and Human Services, Public Health Service	Treating Tobacco Use and Dependence: 2008 Update. Content last reviewed June 2015. Agency for Healthcare Research and Quality, Rockville, MD. http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/index.html

GENERAL RESOURCES FOR HEALTH PROFESSIONALS

Organization	Website/Resource
American Academy of Family Physicians (AAFP)	Ask and Act Smoking Cessation Program: http://www.aafp.org/about/initiatives/ask-act.html
American College of Chest Physicians (ACCP)	Toolkit: http://tobaccodependence.chestnet.org/
Association for the Treatment of Tobacco Use and Dependence (ATTUD)/Council for Tobacco Treatment Training Programs (CTTTP)	<ul style="list-style-type: none"> • http://www.attud.org/ • Accredited training programs: http://ctttp.org/accredited-programs/
National Behavioral Health Network	https://www.bhthechange.org/
RxForChange: Clinician-Assisted Tobacco Cessation	http://rxforchange.ucsf.edu/
Smokefree.gov	http://smokefree.gov/health-care-professionals
Treatobacco.net	http://www.treatobacco.net/en/index.php
U.S. Department of Health and Human Services-Surgeon General Reports	https://www.surgeongeneral.gov/library/reports/index.html
U. S. Preventive Services Task Force (USPSTF)	Final Update Summary: Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavioral and Pharmacotherapy Interventions. U.S. Preventive Services Task Force. September 2015. https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions1?ds=1&s=Tobacco smoking cessation in adults

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PRINCIPLES OF SMOKING CESSATION AND CANCER SURGERY

- **Smokers who need surgery should be treated with evidence-based smoking cessation therapy, including pharmacotherapy and behavior therapy, in order to improve surgical outcomes and long-term cessation rates. There is substantial evidence that smoking cessation with either counseling or pharmacotherapy alone is less effective than the combination of the two.**
 - ▶ **For primary therapy and follow-up recommendations, [see SC-4](#). Preoperative pharmacotherapy options include:**
 - ◊ **If <7 days to surgery, combination NRT preferred (category 1) or varenicline with an early quit date (before day 8).**
 - ◊ **If ≥7 days to surgery, either combination NRT (category 1) or varenicline (category 1) with a day 8+ quit date.**
 - ▶ **There is no clear evidence that NRT degrades the wound healing benefits of smoking cessation. NRT offers benefits over continued smoking.**
- **Smoking increases the risk of pulmonary complications, surgical site infection, and poor wound healing in patients undergoing surgery. [See Smoking-Associated Risks for Patients With Cancer \(SC-B\)](#). Quitting smoking reduces these complications. There is no evidence that quitting smoking shortly before surgery increases the risks of any complications.**
- **Patients should be encouraged to quit smoking as soon as possible before surgery, regardless of how short the time to surgery is.**
- **Longer periods of smoking cessation confer better surgical outcomes but should not delay appropriate timing for cancer resection.**
- **There is insufficient evidence to support delaying a quit attempt at anytime prior to surgery.**
- **Although quitting smoking reduces surgical risk, access to cancer surgery should not be restricted for smokers.**

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**PRINCIPLES OF BEHAVIORAL STRATEGIES**

- **Pharmacotherapy is most effective when combined with behavior therapy.**¹ Population-level studies of smoking cessation treatment modalities indicate that counseling by a smoking cessation specialist plus medication results in a significant improvement in cessation rates relative to no counseling or medication (OR = 3.25; CI, 2.05–5.15).² In addition to the benefits of enhancing motivation and knowledge of the addiction process, behavior therapy assists patients with medication use and strategies since adherence to tobacco treatment medication recommendations is often inadequate. Therefore, pharmacotherapy alone without some form of counseling may not be better than unaided cessation.
- **Through behavior therapy, smokers are provided with problem-solving skills, support, and encouragement. Behavior therapy, tailored somewhat to the patient's nicotine dependence and previous quit attempts, provides strategies for:**¹⁻³
 - ▶ Coping with nicotine withdrawal symptoms and cravings (Note: Symptoms typically peak within 2 weeks after quitting and then subside.)
 - ▶ Identifying smoking triggers
 - ▶ Coping with stressful and difficult situations in which smoking is likely
 - ▶ Avoiding high-risk situations
 - ▶ Addressing other patient-specific barriers to and facilitators of smoking behavior change
- **Motivational counseling is beneficial for all patients, but is essential for those not yet ready to quit.**³⁻⁵
 - ▶ Motivational counseling involves first establishing a connection with the patient and then exploring the smoker's feelings (eg, distress), beliefs (eg, fatalistic), and values (eg, importance of family) in order to help him/her work through ambivalence or conflicting motivations about quitting. Clinicians use a guiding and empathetic style to help the smoker: 1) understand his/her reasons for quitting and smoking; 2) understand the relation of these to his/her values and goals; and 3) build his/her confidence to quit and stay quit. To achieve this, clinicians ask open-ended questions, reflect back patient comments, affirm patient strengths, and summarize discussion. Clinicians should express acceptance for the patient and validate his/her worth, strengths, and independence.
 - ▶ Physicians and health professionals use four basic strategies, commonly referred to as OARS, for motivational interviewing: Open-ended questions; Affirmations; Reflective listening; and Summary statements.
 - ▶ For patients who struggle to identify reasons to quit, the clinician can also use the 5 R's strategy focusing on: the personal Relevance of quitting; personal Risks of continuing smoking; personal Rewards of quitting; identifying Roadblocks to quitting; and Repeating the message at every contact.³
- **In smokers with cancer, there is a high incidence of depression, anxiety, and stress, all of which are common causes of relapse. Providers should routinely assess for these symptoms among smokers throughout treatment for tobacco dependence. It may be optimal to enroll patients in a behavior therapy program with specific interventions designed to ameliorate these conditions and other cancer-related relapse challenges. This may require referral to specialized smoking cessation programs that have staff trained to treat mental health disorders, or referral to behavior therapists who have expertise in treating comorbid substance dependence and mental health disorders.**
- **Specialized treatment centers may consider providing smoking cessation therapy targeted specifically to patients with cancer (eg, individual therapy and group support that focuses on challenges specific to cancer survival and treatment) with access to counselors or group leaders experienced in the treatment of patients with cancer.**

[References on next page](#)**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



PRINCIPLES OF BEHAVIORAL STRATEGIES

Behavior Therapy/Counseling Recommendations:

- **Four or more sessions during each 12-week course of pharmacotherapy. The first session is recommended within 3 weeks of cessation (within 1 week preferred).**
 - ▶ **Duration: 10–30+ minutes per session. Research suggests that longer, more frequent sessions are linked to higher success rates.**
 - ▶ **At a minimum, brief advice should be delivered. Brief advice of about 3 minutes by physicians or other health care providers results in a small but important increase in quit rates.³**
- **Individual or group therapy, in-person and/or by phone, in coordination with a smoking cessation clinic if available.**
 - ▶ **For those in active cancer treatment, behavior therapy can occur during scheduled oncology visits to avoid the need for additional appointments.**
 - ▶ **Refer to a smoking cessation quitline, in addition to providing brief counseling from a health care provider, if face-to-face or group intervention is not available. [See Smoking Cessation Resources \(SC-C\)](#).**
- **Should be performed by a tobacco treatment specialist or a dedicated staff member (ie, nurse, medical assistant, health educator) trained in smoking cessation motivational and behavior strategies.**
- **Therapy should include skills training, social support, and motivational interviewing with print- or web-based patient education materials.**
- **For more information on behavior therapy for smoking cessation, [see Discussion](#).**

References

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Smoking Cessation

PRINCIPLES OF SMOKING CESSATION PHARMACOTHERAPY

- Smoking cessation is important for improving clinical outcomes for patients with cancer. Therefore, the included agents and methodologies should be made available to all patients with cancer who smoke.
- A minimum of 12 weeks of combination NRT or varenicline^a is recommended for the initial quit attempt. Therapy may be extended to 6 months or longer to promote continued cessation while attempting to avoid longer periods of time if possible. Varenicline can be used up to 1 year for continued abstinence.
 - ▶ Follow-up is recommended (in-person or by phone) within 2 weeks after starting pharmacotherapy, but can be extended to within 3 weeks to coordinate with regularly scheduled oncology appointments as needed. Additional periodic follow-up during therapy (at a minimum of 12-week intervals), and after completion of therapy, is recommended.
 - ▶ Nicotine withdrawal symptoms typically peak within 2 weeks of quitting and then subside. Encourage continued therapy through brief slips. Patients who do not quit immediately may quit at some later point after withdrawal symptoms subside.
 - ▶ Pharmacotherapy dose adjustments may be considered as clinically indicated.
- Track attempts at smoking reduction. If reduction efforts stall, or reaching total abstinence seems unlikely, consider switching to a different pharmacotherapy.
- As patients progress through multiple lines of treatment, behavior therapy should be progressively intensified with referral to specialty care (eg, psychiatrist, psychologist) as indicated.

Preferred Primary Therapy Options	<ul style="list-style-type: none"> • Combination NRT: Nicotine patch + short-acting NRT (lozenge/gum/inhaler) or • Varenicline^{a,b} • For patients who continue to smoke or experience relapse: Evaluate use of current therapy and consider continuing or resuming the initial pharmacotherapy, or switch to the other primary therapy option before trying the subsequent therapy options.
Subsequent Therapy Options*	<ul style="list-style-type: none"> • Combination NRT + bupropion (sustained release)^b • Bupropion (sustained release)^b

*Additional pharmacotherapy options are currently being evaluated. See [Discussion](#) for details.

[Continued](#)

^aNausea is a common side effect of varenicline and may need to be managed for patients with cancer, especially during chemotherapy.

^bBupropion should be avoided for patients with brain metastases due to seizure risk. Varenicline should be used with caution for those with seizure risk.

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Smoking Cessation

PRINCIPLES OF SMOKING CESSATION PHARMACOTHERAPY

- In most circumstances, the side effects related to preferred smoking cessation medications are minimal and are considered an acceptable risk compared to smoking. Serious side effects are extremely rare. Refer to manufacturer inserts for exhaustive lists of potential side effects and warnings.^f
- A multicenter randomized controlled trial (RCT) examined the neuropsychiatric safety of varenicline and bupropion in 2 cohorts of patients: those with diagnosed psychiatric disorders (n = 4074) and those without (n = 3984). Rates of neuropsychiatric adverse events in individuals receiving varenicline or bupropion were not significantly increased relative to those receiving nicotine patches or placebo in either cohort.^g

	Standard Dose ^c	Duration	Adverse Effects and Contraindications ^{f,g}
Combination NRT (preferred)	<ul style="list-style-type: none"> • Begin with 21 mg patch + short-acting NRT^d • If 21 mg patch is not effective, consider using more than one patch to increase the dose to 35 or 42 mg • Short-acting NRT every 2 hr (while awake), or more often as needed 	12 wk ^e	<p>Blood nicotine levels from NRT, including combination NRT, are significantly less than from smoking cigarettes. NRT is well tolerated and nicotine toxicity is rare and transient, even when used with smoking. Patients commonly under-dose when using combination NRT. Nicotine overdose is rare, but possible and usually short-lived.</p>
Varenicline (preferred)	<ul style="list-style-type: none"> • Initiate dosing 1–2 wk prior to quitting • Days 1–3: 0.5 mg orally, once daily • Days 4–7: 0.5 mg orally, twice daily • Day 8 to end of treatment: 1 mg orally, twice daily, if tolerated 	12 wk ^e	<ul style="list-style-type: none"> • Nausea is a common side effect of varenicline and may need to be managed for patients with cancer, especially during chemotherapy. • Although these side effects are uncommon, providers should monitor for the development or worsening of serious neuropsychiatric issues (ie, depression and suicidal ideation/behavior), including for patients without a previous history, and discontinue use if these signs occur. • Use with caution for patients with seizure risk.
Bupropion (sustained release) ± NRT	<ul style="list-style-type: none"> • Initiate dosing 1–2 wk prior to quitting • Days 1–3: 150 mg orally, once daily <ul style="list-style-type: none"> ▶ Adjust dose for hepatic insufficiency. • Day 4– end of treatment: 150 mg orally, twice daily, if tolerated • Maximum 300 mg per day 	7–12 wk ^e	<ul style="list-style-type: none"> • Although these side effects are uncommon, providers should monitor for the development or worsening of serious neuropsychiatric issues (ie, depression and suicidal ideation/behavior), including for patients without a previous history, and discontinue use if these signs occur. See Manufacturer Black Box Warning, and weigh the substantial benefits of immediate smoking cessation versus risks of increased hostility, depression, or suicidal behavior. • Bupropion is contraindicated for patients with seizure risks (ie, stroke, brain metastases), those taking MAO inhibitors (increased risk of hypertensive reactions) or tamoxifen, or those with closed-angle glaucoma.

^cDose adjustments may be considered if clinically indicated.

^dGradually decrease dose over 10 weeks or more. Dose reduction may not be appropriate for patients with limited life expectancy.

^eTherapy may be extended to promote continued cessation (ie, 6 mo–1 y).

^fFor drug labels and full prescribing information for varenicline, bupropion, and NRT products, refer to the National Institutes of Health website at <https://dailymed.nlm.nih.gov/dailymed>.

^gAnthenelli RM, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet* 2016;387:2507-2520.

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 08/21/17

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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Overview

Nearly 40 million adults in the United States currently smoke cigarettes, accounting for approximately 15% of the adult population in 2015—16.7% of males and 13.6% of females.¹ Cigarette smoking results in over 480,000 premature deaths yearly, and 1 in every 5 deaths are smoking-related.² Tobacco smoking has been implicated in causing cancers of mouth, lips, nose, sinuses, larynx, pharynx, esophagus, stomach, pancreas, kidney, bladder, uterus, cervix, colon/rectum, ovary, and myeloid leukemia.³ Cancers linked to tobacco use comprise 40% of all cancer diagnoses and cigarette smoking is linked to 30% of all cancer deaths nationwide.⁴ State-level data suggest that cigarette smoking is responsible for as high as 40% of cancer deaths in some geographic regions.⁵ Lung cancer is the leading cause of cancer death in both men and women.⁴

These guidelines emphasize the importance of smoking cessation in all patients with cancer and seek to establish evidence-based, standard-of-care recommendations tailored to the unique needs and concerns of patients with cancer. The recommendations contained herein describe interventions for cessation of cigarette smoking. However, the panel recommends that patients with cancer be encouraged to discontinue use of all combustible products (eg, cigars, hookah, marijuana) as well as smokeless tobacco products.

In a 2014 report from the Surgeon General, *The Health Consequences of Smoking—50 Years of Progress*, a comprehensive review of the evidence revealed the following important findings for patients with cancer and cancer survivors:²

- Sufficient evidence exists to infer a causal relationship between cigarette smoking and adverse health outcomes, increased all-cause mortality (ACM), and cancer-specific mortality.

- Sufficient evidence exists to infer a causal relationship between cigarette smoking and second primary cancer.
- Evidence is suggestive of a causal relationship between cigarette smoking and risk of recurrence, poorer response to treatment, and increased treatment-related toxicity.

Although the harmful effects of smoking after a cancer diagnosis have been clearly demonstrated, many patients continue to smoke cigarettes during treatment and beyond. The prevalence of continued smoking among those who have received a cancer diagnosis has been examined in recent studies. The rate of smoking post-diagnosis varies widely by cancer type and with other factors such as gender, race, and age.

Smoking Prevalence in Patients with Cancer

Using data from the National Health and Nutrition Examination Survey (NHANES), of the 566 cancer survivors who regularly smoked prior to their diagnosis, 64% continued to smoke post-diagnosis. Those identified at higher risk for continued smoking included female, younger, and Hispanic individuals.⁶ In the Cancer Care Outcomes Research and Surveillance (CanCORS) cohort of patients with lung (n = 2456) and colorectal (n = 3063) cancers, 90% of patients with lung cancers and 55% of patients with colorectal cancer reported a history of smoking. At diagnosis, 39% of those with lung and 14% of those with colorectal cancer were current smokers, and of these individuals 14% of patients with lung and 9% of patients with colorectal cancer continued to smoke at 5 months post-diagnosis.⁷

Smoking often persists beyond cancer treatment and well into survivorship. In a population-based study using the Behavioral Risk Factor Surveillance System, survivors of tobacco-related cancers had a



smoking prevalence of 27% compared with 16% and 18% for other cancer survivors and those without a history of cancer, respectively.⁸ Based on prospectively collected data from 772 individuals with cancer in the Cancer Prevention Study-II Nutrition Cohort, persistent smoking was observed in 68.7% and 57% of the cohort at 2 and 4 years post-diagnosis, respectively.⁹ One study revealed smoking prevalence to be highest among survivors of bladder, lung, and ovarian cancers.¹⁰ Other studies have found high prevalence of continued smoking in survivors of cervical cancers.¹¹

Health Care Community Response

Given the adverse health effects and prevalence of smoking in patients with cancer and survivors, several leading national organizations have called upon the oncology community for improved smoking cessation efforts. In 2013, the American Association for Cancer Research (AACR) released a policy statement calling for provision of evidence-based smoking cessation assistance to all patients with cancer, outlining the following objectives:

- “Universal assessment and documentation of tobacco use by cancer patients in all clinical settings;
- Development of universal standards for measurement of tobacco use and exposure in clinical and research settings;
- Incorporation of evidence-based tobacco interventions into review criteria used by research and health care quality and accreditation bodies; and
- Recognition and support of the value of tobacco cessation interventions by health systems, payers, and research funders through provision of appropriate incentives for infrastructure development and intervention delivery.”¹²

Additionally, in a recent policy statement update, ASCO called upon oncology professionals to treat tobacco dependence as aggressively and compassionately as cancer and to advocate for the wide availability of tobacco cessation services.¹³

However, despite general consensus on the importance of smoking cessation, particularly for patients with cancer, many cancer centers and oncology practices report that they fall short of providing consistent, high-quality smoking cessation services. In a survey of 58 NCI-designated cancer centers, 20% reported offering no smoking cessation services for their patients, 38% did not routinely provide tobacco education materials to patients, and only half reported that they effectively identified tobacco use in their patients.¹⁴ The AACR Task Force on Tobacco and Cancer found that few cancer care institutions utilize systematic and consistent mechanisms to foster cessation among patients with cancer.¹²

Several studies have linked increased patient satisfaction to the delivery of smoking cessation advice or intervention.^{15,16} Data from large surveys of oncologists practicing in academic medical centers, non-academic hospitals, and oncology practices depict generally high rates of smoking assessment and providing initial advice to quit.¹⁷⁻²⁰ However, smoking assessment rates were weaker outside of the academic/university setting (ie, for those practicing in a hospital-based, nonacademic, or private setting).²⁰ Regardless of work setting, only 30% to 44% of respondents reported discussing specific interventions or providing subsequent follow-up. Moreover, the majority of respondents report inadequate training and/or a lack of confidence in ability to provide effective smoking cessation counseling and intervention.¹⁷⁻²⁰ A dearth of smoking assessment and documentation has also been demonstrated in oncology trials.^{21,22}

Issues regarding insurance coverage and provider reimbursement for smoking cessation assessment, counseling, and cessation aids have also presented a challenge for the oncology community in the past. However, implementation of the Affordable Care Act has led to changes designed to increase access to smoking cessation interventions.²³

Barriers to Smoking Cessation in Oncology Patients

Patients may have limited awareness about the harms associated with continued smoking upon a diagnosis of cancer. A recent survey assessed knowledge of the harms of continued smoking in 985 current or former smokers with a cancer diagnosis.²⁴ Across the board, one half to three-quarters of the respondents were unaware of the negative impact that smoking can have on chemotherapy, radiation, surgery, overall treatment efficacy, survival, and development of second primary cancers. The knowledge gap was most prevalent among those with non-tobacco-related cancers and those who were actively smoking at diagnosis.

Although over 68.8% of current smokers in the United States express a desire to quit and 52.5% report making a quit attempt within the past year, only 6.2% report recent smoking cessation.²⁵ In the general population, individuals who smoke report a number of different barriers to quitting, including stress; dependence; home, work, and social environmental factors; and lack of resources and support for quitting.²⁶ Importantly, patients and providers in the oncology setting face additional life challenges that can amplify the magnitude of these barriers.

In a population-based analysis of individuals recently diagnosed with cancer who actively smoked, health professional-provided cessation counseling was provided to only 52% of individuals in the past 12 months.²⁷ Surveys of oncology providers have identified common

themes among barriers to smoking cessation for patients with cancer. Inadequate provider training and lack of time are often cited by oncology providers as barriers to successful intervention.¹⁸ Providers have also cited patient-related factors such as inability to quit, lack of motivation, or resistance to treatment.^{17,18} However, pain, second-hand smoke exposure, guilt over smoking, fear of stigmatization, and fatalism regarding disease also represent obstacles unique to oncology patients, particularly those with advanced disease.²⁸⁻³³

Notably, clinical trial research on smoking cessation for patients with cancer is limited, particularly for patients thought to have non-tobacco-related cancers. Barriers that limit or prevent enrollment in smoking cessation trials include smoking rate, medical history, contraindicated medications, lack of interest, and language barriers.³⁴ Ongoing randomized controlled trials (RCTs) are examining smoking cessation interventions designed specifically for patients with cancer.^{35,36}

Given the complexity of smoking cessation interventions for patients with cancer, there is a great need for resources that provide guidance on smoking cessation specifically for this patient population. The inaugural NCCN Guidelines for Smoking Cessation have been created to establish a standard of care for smoking cessation in patients with cancer. The NCCN Guidelines panel has developed these guidelines in order to facilitate implementation of this standard, to allow for quality control monitoring, to fill a gap among existing treatment guidelines, and ultimately, to improve the health and outcomes for patients with cancer.

Literature Search Criteria and Guidelines Update Methodology

Prior to the development of this inaugural version of the NCCN Guidelines® for Smoking Cessation, an electronic search of the PubMed database was performed to obtain key literature in smoking

cessation for patients with cancer, published from December 2015 through December 2016, using the following search terms: (smoking cessation[Title/Abstract] OR quit smoking[Title/Abstract] AND (cancer[Title/Abstract] OR oncology[Title/Abstract])). The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.³⁷

The search results were narrowed by selecting studies in humans published in English. The PubMed search resulted in 220 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the NCCN Guidelines update meeting as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN [webpage](#).

General Principles of the Smoking Cessation Guidelines

The recommendations in these guidelines apply to cessation of cigarette smoking for patients with cancer; however, the panel strongly recommends that patients also discontinue use of all combustible products, including cigars, hookah, marijuana, as well as smokeless tobacco products. Smoking cessation has health benefits even after a cancer diagnosis, regardless of stage or prognosis—namely improvement in cancer treatment outcomes, disease recurrence, and secondary cancers. Importantly, a diagnosis of cancer may present a

teachable moment and valuable opportunity for providers to encourage smoking cessation.^{9,38-40} It is the view of the NCCN Guidelines panel that it is never too late for patients with cancer at any stage to stop smoking cigarettes and experience health benefits.

Because smokers with cancer often demonstrate high-level nicotine dependence, the panel recommends a multimodal approach to cessation therapy. The NCCN Panel recommends that treatment plans for all smokers with cancer include the following 3 tenets: evidence-based motivational strategies and behavior therapy (counseling), which can be brief; evidence-based pharmacotherapy; and close follow-up with retreatment as needed.

The panel asserts that a smoking cessation approach combining pharmacologic therapy and behavior therapy is the most effective and leads to the best results for smoking cessation. The two most effective pharmacotherapies are combination nicotine replacement therapy (NRT) (combined long- and short-acting NRT) and varenicline. There is a dose-response relationship for the success of counseling; high-intensity behavior therapy with multiple counseling sessions is most effective, but at least a minimum of brief counseling is needed and effective.⁴¹⁻⁴⁴ Quitlines may be used as an adjunct, especially in lower-resource settings.^{45,46}

The panel also emphasizes the importance of documenting smoking status and treatment plans in the patient health record. Patient health records should be updated at regular intervals to indicate changes in smoking status, quit attempts made, and interventions utilized.

The panel emphasizes that smoking relapse and brief slips are common. Providers should discuss this with patients and provide guidance and support to encourage continued smoking cessation

attempts despite slips. Additionally, providers should be aware that smoking slips do not necessarily indicate a need for an alternative intervention. More than one quit attempt with the same therapy may be necessary to achieve long-term cessation.

Finally, smoking cessation interventions should be offered and continued throughout the oncology care continuum, including during end-of-life care. Emphasis on patient preferences and values is important when considering the best approach to fostering smoking cessation in that setting.

Smoking-Associated Risks for Patients with Cancer

Exposing cancer cells to cigarette smoke has been shown to promote a more malignant phenotype through its effects on angiogenesis and cell proliferation, migration, invasion, and survival. For a review of the preclinical data, see Sobus and Warren (2014).⁴⁷ These data have been corroborated by clinical studies. Per the Surgeon General's Report, *The Health Consequences of Smoking—50 Years of Progress*², sufficient evidence exists to support a causal relationship between smoking and adverse health outcomes, increased ACM and cancer-specific mortality, and increased risk for secondary primary cancers. Additionally, existing evidence is suggestive of a link between smoking and increased risk of cancer recurrence, poor treatment response, and increased treatment-related toxicity.

NCCN recommends that providers should inform patients of the potential benefits of smoking cessation, including improved survival, treatment outcomes, and health-related quality of life, as well as decreased treatment-related toxicity, drug side effects, and surgical complications. Patients should receive education on the specific risks of smoking during treatment for their particular cancer and should be encouraged to stop smoking as far in advance as possible before

initiating cancer treatment. All members in the household who smoke should be encouraged to quit for the benefit of the patient. Prior to initiating treatment, when making decisions regarding treatment selection, dosage, and timing of initiation, providers should consider patient smoking status and potential smoking-related effects.

Overall Survival and Mortality

Smoking has been linked not only to the development of disease in tobacco-related cancers, but also to prognosis upon diagnosis and risk of death during treatment. Evidence suggests that current smoking increases risk of death and negatively impacts survival for patients with cancer in a variety of disease sites, including bladder,⁴⁸⁻⁵¹ breast,⁵²⁻⁵⁴ cervix,^{55,56} colon/rectum,⁵⁷⁻⁵⁹ endometrium,⁶⁰ esophagus,^{61,62} head and neck,⁶³⁻⁶⁶ kidney,⁶⁷⁻⁶⁹ lung,⁷⁰⁻⁷³ ovarian,⁷⁴ pancreas,^{75,76} and prostate,⁷⁷ as well as hematologic malignancies.⁷⁸

Prospective studies of smoking at cancer diagnosis offer insight into the negative effects of smoking on overall survival (OS), disease-specific mortality (DSM), and ACM. In the 2014 Surgeon General's report, a comprehensive review of the data assessing smoking and ACM in patients with cancer revealed that 87% of the studies (139/159) indicated increased risk, while 62% of all studies (99/159) demonstrated a statistically significant risk increase.² Additionally, over half of the reviewed studies found at least a 50% increase in risk of death.² Additionally, among the studies examining OS in patients with cancer who smoke, 77% (48/62) were indicative of shortened survival, with 42% (26/62) revealing statistical significance.² Finally, smoking in patients with cancer was associated with higher DSM in 79% of studies reviewed (46/58), with a statistically significant link between cancer-related mortality and patients' smoking status in 59% (34/59).²

Risk of Recurrence or Secondary Primary Tumor

A number of studies have linked cigarette smoking and heightened risk of recurrence (ie, recurrent cancer in the same anatomic location as the original primary cancer). The 2014 Surgeon General's Report identified a positive association between smoking and risk of recurrence in 82% of the reviewed studies (42/51), with 53% of studies revealing significantly increased risk.² Among the studies that compared relative risk (RR) of recurrence between never smokers, former smokers, and current smokers, the median RR was 1.42 and 1.15 for current and former smokers, respectively.²

Disease sites with data linking current patient smoking to increased risk of recurrence include the anus,⁷⁹ bladder,^{48,80,81} breast,⁸² lung,⁷⁰ stomach,⁸³ and prostate.^{77,84-86}

Studies have also examined the impact of continued smoking in patients with cancer on the risk of second primary tumor formation. The 2014 Surgeon General's Report identified a positive association between smoking and risk of second primary tumor in all studies examined (n = 26). The association was strongest when considering the effects of smoking on RR of developing a smoking-related second primary cancer (eg, lung cancer). Among 5 studies classifying smoking status into "never," "former," and "current," the median elevated RR of a second primary tumor was 1.20 and 2.20 for former and current smokers, respectively. Data from a large retrospective series and pooled data analyses have continued to provide support for smoking and increased risk of second primary malignancy, especially smoking-associated cancers.^{87,88} Additionally, data also suggest that smoking interacts synergistically with radiation therapy (RT) to elevate the risk of second primary cancers.^{2,89,90}

Smoking-Related Effects on Treatment Efficacy, Side Effects, and Outcomes

A majority of the existing data establishes and supports the detrimental impact of persistent smoking during cancer treatment. In a 2014 report from the Surgeon General, 80% of the evaluated studies (66/82) demonstrated a statistically significant association between active smoking and increased anticancer treatment-related toxicity.² Smoking has implications across the spectrum of cancer treatment, including surgical outcomes, RT efficacy and toxicity, chemotherapy metabolism and side effects, and overall symptom burden. This discussion also addresses the developing evidence base for the benefits of smoking cessation after receiving a cancer diagnosis.

Smoking-Associated Risks

Surgery

Smoking has been shown to negatively impact outcomes from cancer surgery, affecting postoperative complications, quality of life, length of hospital stay, and mortality risk.

In lung cancer, studies show that smoking impacts the success of surgical resection, decreases postoperative quality of life, and increases persistent dyspnea and thoracic pain at 12 months postoperatively.^{91,92} Analysis of data from 7990 patients who had primary resections for lung cancer (Society of Thoracic Surgeons General Thoracic Surgery Database) revealed increased risk of hospital death and pulmonary complications associated with smoking.⁹³

The adverse effects of smoking on postoperative outcomes was examined in more than 20,000 patients with gastrointestinal (n = 12,432), lung (n = 4490), and urinary tract cancers (n = 3491) using the Veteran's Health Administration Surgical Quality Improvement Program

(VASQIP) database for 2002 through 2008.⁹⁴ Surgical complications examined included surgical site infections, vascular complications (ie, venous thromboembolism, stroke/cerebrovascular accident, myocardial infarction), and composite pulmonary outcomes (CPO: pneumonia, failure to wean from ventilator >48 hours, or re-intubation for cardio-respiratory failure). Across all three cohorts, never smokers had fewer complications than former and current smokers. Compared with prior smokers, current smokers in the gastrointestinal cancer cohort had higher postoperative rates of pneumonia, failure to wean from ventilator, reintubation, and CPO. In the lung cancer cohort, current smokers had higher rates of pneumonia, failure to wean from the ventilator, reintubation, CPO, and return to surgery compared with former smokers. Current smoking status was associated with an increased length of hospital stay across all cancer sites when compared with never smokers; never smokers and prior smokers did not differ on this measure.

Postsurgical outcomes (ie, incisional infections, infectious and major complications, and mortality at 30 days) were compared between cohorts of never smokers, former smokers, and current smokers using data from over 26,000 patients with colorectal cancer in the American College of Surgeon's National Surgical Quality Improvement Program database (2005–2010). Postoperative morbidity and mortality rates were higher among current smokers and a significant dose-dependent effect was observed when stratifying risk of major complications by pack-years of smoking.⁹⁵

In patients undergoing hematopoietic stem cell transplantation to treat acute leukemias, pulmonary complications, and longer postoperative hospital stays were more commonly observed in patients who smoked.⁹⁶

Smoking can also impair wound healing and predispose patients to surgical complications for those undergoing reconstructive surgeries after cancer treatment. Among patients with breast cancer who underwent transverse rectus abdominis myocutaneous (TRAM) flap breast reconstruction surgery, smoking was associated with significantly higher risk of flap complications and delayed healing,^{97,98} and evidence suggested that complication risk was reduced by smoking cessation of at least 4 weeks prior to surgery.⁹⁷ In patients with stage III or IV squamous cell carcinoma of the head and neck, serum cotinine concentration was dose-dependently linked to increased risk of wound complications following reconstructive head and neck surgery.⁹⁹

Radiation

Studies have shown that prior smoking and active smoking during RT may decrease treatment response and increase complication rates, particularly for patients with head and neck cancers, but also in cervical, lung, breast, or prostate cancers.

In patients with head and neck cancer receiving RT, current smokers had poorer rates of locoregional control.^{64,100} In another cohort, patients with head and neck cancer who continued to smoke during RT had lower rates of complete response and worse survival times than nonsmokers or those who quit prior to treatment.¹⁰¹ Continued smoking during RT in patients with head and neck cancer has also been shown to increase the rates of treatment-related complications. In patients with laryngopharyngeal cancers, smoking during treatment was associated with significantly elevated incidence of osteoradionecrosis and hospitalization during treatment.¹⁰² Another study demonstrated a significantly greater decline in several health-related quality-of-life measures in patients who continued to smoke during therapy compared with patients who quit beforehand.¹⁰³

Among 3,489 patients receiving RT as part of treatment for stage I or II cervical cancer, heavy smoking (defined as at least 1 pack/day) was the strongest independent factor in predicting long-term major bladder, rectal, or small bowel complications, with even light/moderate smoking (less than 1 pack/day) predisposing patients to small bowel complications.¹⁰⁴ In another study of 565 patients with cervical cancer who were receiving primary RT, patients who smoked during treatment had lower cure rates, higher frequency of RT side effects, and higher rates of severe, irreversible complications.¹⁰⁵

Smoking during RT for non-small-cell lung cancer was associated with significantly decreased locoregional control.¹⁰⁶ Active smoking may also decrease the efficacy of RT for prostate cancers and increase the prevalence of long-lasting treatment-related effects on the bowel and anal sphincter.¹⁰⁷⁻¹⁰⁹ Concurrent smoking and RT increased the risk of cardiovascular disease in 4414 10-year survivors of breast cancer.¹¹⁰

Chemotherapy/Systemic Therapy

Data on the impact of smoking on chemotherapy are much more limited than that for surgery and RT, in part because smoking quantity during treatment is often left out of the medical record.²¹ Many of the purported effects of smoking during chemotherapy are extrapolated from what is known about the impact of chemotherapy and smoking as individual factors of health. Smoking has the potential to exacerbate the risk of anticancer drug-related pulmonary and cardiac toxicities such as cardiomyopathy and pulmonary fibrosis.¹¹¹ Combining neoplastic agents with radiation while smoking may lead to further toxicity. Additionally, cancer drug side effects such as weight loss, cachexia, and fatigue may also be increased by smoking during treatment.^{111,112}

Many systemic anticancer agents result in some degree of immune suppression/compromise, and smoking during chemotherapy may

further compromise immune function in an already vulnerable patient population.^{21,111} Preclinical and clinical studies suggest that smoking and nicotine exposure can be detrimental to the function of both the adaptive¹¹³⁻¹¹⁶ and innate immune system.¹¹⁷⁻¹²¹ Similarly, cigarette smoking may increase the incidence of infection, particularly for smoking-related infectious diseases such as pneumonia and influenza.¹²²

Preclinical studies also suggest a potential link between nicotine exposure from smoking and the development of chemoresistance,¹²³⁻¹²⁷ although no clinical data are currently available to support these findings.

Smoking can also impact the metabolism of certain cytotoxic chemotherapies and other systemic therapy. Smoking effects on cytochrome P450 enzymes may alter drug clearance time and plasma concentration, potentially impacting the efficacy of certain drugs for patients who smoke.¹²⁸ Providers should consider whether patients are at risk for altered drug metabolism due to smoking and determine if medication or dose adjustments may be required.

Drugs with metabolisms that are known to be affected include erlotinib and irinotecan. Rapid drug clearance has been observed in smokers who were receiving erlotinib therapy, such that higher doses may be required to achieve equivalent systemic exposure to standard dosing in nonsmokers.^{129,130} Similarly, smoking increases the clearance time of irinotecan, potentially lessening systemic exposure.^{129,131} Given the narrow therapeutic index of systemic therapy for lung cancer, small changes in drug exposure due to smoking could affect treatment efficacy and patient outcomes.¹²⁹ Bendamustine metabolism is also likely to be impacted by smoking, resulting in decreased drug plasma concentration and increased concentration of its active metabolites.^{132,133}

However, smoking does not appear to alter the pharmacokinetic properties of taxane chemotherapeutics (eg, docetaxel, paclitaxel) despite its paradoxical protective effects on drug-induced neutropenia and leukopenia.¹³⁴

Symptom Burden

In a study of 947 patients who were undergoing chemotherapy and/or RT, smoking during treatment was linked to a higher overall burden of symptoms commonly experienced among patients with cancer. In analyses that controlled for age, gender, race, education, occupation, treatment, cancer site, and Karnofsky performance score, current smokers had a significantly higher symptom burden compared with nonsmokers, both during treatment and 6 months afterwards.¹³⁵ Active smoking in patients with advanced lung cancer was associated with greater symptom burden on diagnosis and poorer health-related quality of life post-diagnosis.¹³⁶ Additional studies suggest that current smokers with cancer may experience more severe or frequent pain than nonsmoking counterparts.¹³⁷⁻¹⁴⁰

Benefits of Smoking Cessation for Patients with a Cancer Diagnosis

For many smokers, the benefits of smoking cessation can be appreciated immediately through reduced blood carbon monoxide levels, decreased irritative respiratory symptoms (eg, cough, shortness of breath), and improved lung function. In the long term, cessation is associated with reduced risk of smoking-related disease, development of malignancy, and smoking-related mortality.¹⁴¹ Although the deleterious effects of smoking after a cancer diagnosis are well documented and understood, research on the benefits of cessation post-diagnosis is much more limited.^{12,142} For patients with cancer, the potential benefits and risk reductions associated with cessation are of critical importance.

Studies have begun to assess the impact of smoking cessation at or near the time of a cancer diagnosis by comparing outcomes of patients who continue to smoke during cancer treatment to those who quit prior to treatment (“recent quitters”). Studies generally show that recent quitters have survival outcomes intermediate to that of never-smokers and current-smokers, suggesting a measurable benefit of cessation post-diagnosis. The data to support this survival pattern are derived primarily from cohorts of patients with lung or head and neck cancers,^{70,72,101,143-145} but similar patterns have been observed for other disease sites.^{51,72,146}

A recent study of cancer registry data from Japan (n = 30,658) compared the risk of ACM in never smokers, former smokers (>3 years), recent quitters (≤3 years; 85% within the past year), and current smokers.¹⁴⁷ When combined results were weighted by disease site prevalence, risk of death in recent quitters was reduced by 11% compared with current smokers (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.81–0.97). Risk of death in never/former smokers was found to be 15% to 16% lower than current smokers. Over the course of 10 years, adjusted survival rates were consistently higher among recent quitters, former smokers, and never smokers. When comparing recent quitters to former smokers, a small but significant difference in survival rate was observed (+1.8%–2.9%).¹⁴⁷

A prospective longitudinal study examined the impact of smoking at diagnosis in 5185 patients with cancer across 13 disease sites over the course of at least 12 years.⁷² In this study, recent quitters were examined as a specific subset of former smokers who quit within 1 year of the study’s structured smoking assessment, allowing for comparisons to individuals who actively smoked during cancer treatment. For disease sites with larger recent quit cohorts (ie, lung, head/neck cancers), recent quitters had lower overall mortality risk compared with continued

smokers (current smoker vs. recent quitter: lung cancer HR, 1.38–1.42; head/neck cancer HR, 2.11–2.15).⁷² Similarly, a systematic review and meta-analysis of 10 observational studies pointed to a 5-year survival benefit for patients with lung cancer who quit smoking compared to patients who continued smoking (70% vs. 33%).⁷⁰ In a comprehensive cancer center study that controlled for disease characteristics, smoking history, and patient demographics, 250 patients with lung cancer who quit smoking had statistically improved survival time of 9 months over those who continued to smoke through treatment and beyond.¹⁴⁸

Smoking cessation is linked to reduced risk of recurrence and second primary tumor formation. Data from patients with lung and head and neck cancers showed that rates of second primary cancers were lower for patients who quit smoking than for those who continued to smoke after diagnosis.^{144,149,150} In a cohort of patients with colon cancer, active smokers were at significantly greater risk for baseline metastasis, but interestingly, rates among former smokers and never smokers were similar and significantly less in comparison.¹⁵¹

Cessation at or near cancer diagnosis appears to reduce treatment-related complications compared to patients who continued smoking. In patients undergoing lung cancer resection, preoperative cessation mitigated the risk of pulmonary complications and in-hospital mortality. Risk-adjusted odds ratios (ORs) for mortality and pulmonary complications decreased as preoperative cessation time increased from 14 days to 1 month, to 1 to 12 months, and to more than 12 months.⁹³ A retrospective study of 188 patients undergoing reconstructive surgery after treatment for head and neck cancer revealed that preoperative smoking cessation of at least 3 weeks led to lower incidence of wound healing complications than patients who continued smoking.¹⁵²

Cessation has been shown to lead to improvements in various measures of general health and well-being for patients with cancer. Smoking cessation improved performance status at 6 and 12 months post-lung cancer diagnosis over that of continued smokers when adjusting for disease stage, patient demographics, therapy, and comorbidity.¹⁵³ Additionally, patients with cancer who quit smoking benefited from lower rates of smoking-related cardiovascular and pulmonary disease.¹⁵⁴

Evaluation and Assessment of Patient Smoking

These guidelines highlight the importance of evaluating and assessing smoking status and history in patients with cancer. In a recent policy statement, the AACR emphasized the need for universal assessment and documentation of tobacco use by patients with cancer both in the standard clinical setting and in oncology clinical trials.¹² The NCI-AACR Cancer Patient Tobacco Use Assessment Task Force recently published proposed core and extension items to be used for the assessment of tobacco use in patients with cancer enrolled in research trials.¹⁵⁵ However, current practice is suboptimal, as inadequate or inconsistent assessment and documentation of smoking status has been reported both in the care setting and in the context of clinical trials.^{14,22}

Despite the demonstrated adverse effects of smoking during cancer treatment, a large proportion of cancer clinical trials do not collect adequate, up-to-date information regarding patient smoking status and history, particularly for malignancies other than well-known tobacco-related cancers (eg, lung, head and neck cancers).^{21,22} Such assessments are needed to make evidence-based determinations of the impact of smoking on patients, treatment efficacy, and side effects.

In a large study conducted at a comprehensive cancer center, a smoking assessment questionnaire was integrated into the electronic health record (EHR) in order to automatically identify and refer appropriate candidates for onsite cessation services. The smoking assessment items incorporated into the EHR were refined based on analysis of responses from an initial patient screen containing 23 items. Response analysis revealed that the most effective questions for generating referrals included whether 1) patients smoked cigarettes every day, some days, or not at all; and 2) if/what other types of tobacco products were used. For former smokers, it was important to assess the last time a patient smoked a cigarette, “even a puff,” and for established enrollees to the cessation program, what type(s) of cessation aids were being employed.¹⁵⁶ The study revealed that just 3 assessment questions made it possible to efficiently and accurately identify the vast majority (over 98%) of current smokers or those at risk for smoking relapse.

Determining Smoking Status

The NCCN Guidelines for Smoking Cessation advocate for smoking status to be updated in the patient’s health record at regular intervals to indicate any status changes or quit attempts. To do so, the panel recommends the providers initially ascertain: 1) whether the patient has ever smoked, and if so, then regularly assess; 2) whether the patient is a current smoker; and 3) whether the patient has smoked within the past 30 days. All information should be recorded in the medical record. As a follow-up to the initial evaluation, these guidelines direct providers to a tailored patient assessment based on smoking status and history. Specific algorithms for current smokers (patient smoked within the last 30 days), recent quitters (30 days to 1 year prior), and former smokers (≥1 year since patient last smoked) are included. For never smokers or longer-term former smokers, providers should urge patients to remain smoke-free, explaining the benefits of remaining smoke-free. For

recommendations regarding lung cancer screening for current/former smokers, see the NCCN Guidelines for Lung Cancer Screening at www.NCCN.org.

Assessing Smokers

In patients who are current smokers (or those who have smoked in the last 30 days), providers should assess nicotine dependency to understand the chances for success and risk of relapse, and document the findings in the patient’s health record. To assess nicotine dependency, providers should query patients regarding the amount of cigarettes currently smoked per day, the typical amount smoked within the last 3 months, how soon the patient smokes after waking up in the morning, and whether the patient uses other forms of tobacco (eg, pipes, cigars, snuff, e-cigarettes). The Fagerstrom Test for Nicotine Dependence is an alternative standardized tool for assessing nicotine dependence.¹⁵⁷ However, the panel has opted to recommend a more streamlined assessment for use in the oncology setting.

In order to best tailor treatment, providers should also gather information regarding the patient’s history of quit attempts and why they were or weren’t successful. Specifically, providers should ascertain the longest period of abstinence achieved, the date of the most recent quit attempt, what cessation aids were employed, and why these failed. It is important to document the patient’s previous experience with smoking cessation aids, including any medications, behavior therapy, e-cigarettes, quit-lines, websites, smart phone applications, or other media aids. The patient’s perspective on why these aids were unsuccessful—such as medication side effects, continued cravings, or inefficacy—are important pieces of information.

Patient readiness to quit within the next month should be determined. Providers are encouraged to engage patients in a motivation dialog

about smoking and to ensure patients are aware of the disease-specific risks of smoking and benefits of quitting. Educational resources should be provided. The panel recommends that clinicians provide patients with reasons, ideas, and needs for smoking cessation, emphasizing the importance of both encouragement and directness with patients who smoke. When incorporating motivational interviewing (MI) to promote willingness to quit, the panel emphasized the importance of the following general principles: 1) express empathy, 2) develop discrepancy, 3) roll with resistance, and 4) support self-efficacy.^{158,159} For a summary of the methods and data on MI for smoking cessation, see the *Principles of Behavior Therapy* section below.

If patients are not ready to quit within the next month, providers should assess and address patient-reported barriers and concerns regarding cessation. When possible, providers should work with patients to set a near future quit date and/or consider smoking reduction with the goal of cessation in the near future. The panel encourages immediate initiation of pharmacotherapy for targeted smoking reduction with a goal of cessation in the near future. A meta-analysis of 10 randomized trials in 3760 patients with cancer found quit rates to be comparable when comparing abrupt cessation to gradual smoking reduction.^{160,161} Therefore, both options can be used after discussions with the patient. Trial data since then have continued to mirror this trend of comparable success rates with abrupt cessation and gradual reduction.¹⁶² At each visit, providers should reassess readiness to quit and engage in motivational dialog as indicated.

Assessing Former Smokers/Recent Quitters

To evaluate patients who recently quit (30 days to 1 year prior), providers should assess and document the patient's risk of relapse. The panel suggests the following characteristics to identify patients at high risk for relapse: frequent/intense cravings; elevated anxiety, stress, or

depression; cohabitating or working with smokers; quitting within the past year; use of ongoing smoking cessation treatment; and drug/alcohol use or abuse. The panel considers patients demonstrating at least one of these characteristics to be at higher risk for relapse and recommends a management plan tailored to prevent relapse. Providers should discuss risk of relapse with patients and provide guidance and support to promote continued smoking cessation attempts. As indicated, refer patients with anxiety and/or depression to a specialist to manage psychiatric comorbidities.

Management of patients who demonstrate an elevated risk of relapse includes behavior therapy with counseling on relapse risk factors and relapse prevention. Pharmacotherapy can be considered to promote maintenance of abstinence. However, the panel recommends careful consideration of the potential effects of nicotine re-introduction via NRT in patients who have been nicotine free for an extended period of time (ie, ≥ 30 days). Providers should review smoking-associated risks for patients with cancer as well as the health benefits of abstinence. All management plans and counseling should be documented in the patient health record. For patients deemed to be at low risk for relapse, providers should reinforce success and highlight the importance of continued abstinence. Risk of relapse should be reevaluated at subsequent visits.

It is important to regularly reevaluate patients' smoking status and risk of relapse, which can be accomplished in person or by phone. If relapse occurs, patients should be evaluated per the recommendations for current smokers. Additionally, providers should remain aware that patient self-report of smoking status may underestimate the rate of active smoking among patients with cancer, as is evidenced by research comparing self-reported and objective measures.¹⁶³⁻¹⁶⁵ Patients

who remain smoke free should regularly undergo reevaluation with documentation of any risk factor changes.

Smoking Cessation During or After Cancer Treatment

The following recommendations are appropriate for patients who are currently undergoing cancer treatment as well as cancer survivors.

Devising a Treatment Plan

Following assessments, providers should establish a personalized quit plan for each patient that takes into account the patient's nicotine dependency, prior quit attempts and any cessation aids used, and smoking cessation therapy options. Providers should work with patients to set a quit date as soon as possible. Risk of relapse and smoking slips should be discussed with the patient along with reassurance and support for continued cessation efforts should slips occur.

Smoking Cessation and Cancer Surgery

Smoking has been shown to increase the risk of pulmonary and cardiovascular complications, surgical site infection, and poor wound healing in patients undergoing surgery. For an overview of the data, see section on *Smoking-Related Effects on Treatment Efficacy, Side Effects, and Outcomes* in this Discussion. Study findings generally support the benefits of preoperative smoking cessation, which has been shown to reduce postoperative morbidity in patients undergoing surgery for various cancer types.^{93,166-168}

For patients with planned cancer surgery, cessation should occur as soon as possible before surgery, regardless of how short the time to surgery is. There is no evidence to support a harmful effect of quitting any time before surgery. Although longer periods of preoperative smoking cessation may confer better surgical outcomes,^{167,169} the panel emphasizes that patient smoking should not delay appropriate timing for

cancer resection, and access to cancer surgery should not be restricted based on smoking status. Preoperative smoking cessation interventions that combine pharmacotherapy with behavioral therapy may be most effective.¹⁷⁰⁻¹⁷³ NRT at the normal doses has not been shown to negatively affect acute wound healing,¹⁷⁴⁻¹⁷⁶ and therefore functions as a valuable adjunct to perioperative smoking cessation.

Elective procedures, such as plastic surgery reconstruction, may benefit from delaying surgery for a period of time after smoking cessation. At this time, consensus on an optimal time period of preoperative cessation has not been demonstrated through the existing literature.¹⁶⁹ Providing surgery-specific resources and advice for smoking cessation may facilitate smoking reduction or cessation in patients undergoing elective (non-cancer) surgery.^{177,178}

Preferred Primary Therapy Options

Based on clinical trial data of smoking cessation in patients with cancer, the panel recommends a combination frontline approach including pharmacotherapy and behavior therapy for smoking cessation for patients with cancer. Population studies and meta-analyses of randomized or quasi-randomized trial data support the addition of behavior therapy to pharmacotherapy to enhance the rate of success.¹⁷⁹⁻¹⁸¹

Preferred primary therapy options in these guidelines are 1) combination NRT; or 2) varenicline (typical initial duration of 12 weeks). The combination NRT approach includes the use of a nicotine patch plus a short-acting NRT for breakthrough cravings, such as nicotine gum, lozenge, inhaler, or nasal spray. Patients commonly underdose when using combination NRT.¹⁸²⁻¹⁸⁴ Patients should be advised that nicotine overdose is rare but possible, and usually short-lived. Providers should also note that nausea is a common side effect of varenicline and

may need to be managed in patients with cancer who are receiving chemotherapy. Additionally, varenicline and bupropion should be avoided in patients with brain metastases due to increased seizure risk. For discussion of the evidence for individual pharmacotherapeutic regimens, see the section below on *Principles of Pharmacotherapy*.

As a general principle, the panel recommends trying both preferred primary therapy approaches (combination NRT and varenicline) before proceeding to any of the subsequent pharmacotherapy options. See section below on *Treatment for Persistent Smoking or Relapse* for additional details. Pharmacotherapy regimens should always be paired with behavioral counseling.

Follow-up

Assessment of smoking status and toxicity of pharmacotherapy should be performed within 3 weeks of initiating therapy (within 1 week preferred), at 12 weeks. Assessment should continue on a periodic basis moving forward, including within about 12 weeks following completion of pharmacotherapy. Nicotine withdrawal symptoms typically peak within 1 to 2 weeks of cessation before subsiding. Initial follow-up within 2 weeks of initiating smoking cessation therapy is important in order to assess efficacy and toxicity of pharmacotherapy. Patients who do not quit immediately may quit at a later point once withdrawal symptoms subside. Therefore, providers should encourage continued treatment adherence through brief slips, with adjustments to dose or behavior therapy frequency as indicated. Undesirable side effects may also warrant dose adjustments.

When possible, in-person follow-up during planned clinical visits or individual/group therapy sessions is preferred. To minimize the burden on patients in active cancer therapy, behavior therapy can be provided by a trained member of the health care team during oncology visits.

Alternatives include phone contact. During follow-up, providers should assess risk of relapse and, as indicated, consider adjusting the dose and or type of pharmacotherapy. Patients may slip or relapse, which is expected and can be managed. Maintain close follow-up through the duration of therapy. At 12 weeks, assessment of smoking status should be made in person or by phone. For pharmacotherapy courses exceeding 12 weeks duration, assessment should be repeated at the end of the course of therapy.

If patients remain smoke free, additional follow-up should take place at 6 and 12 months, either in person or by phone. Motivational strategies should be employed to promote continued abstinence. Duration of pharmacotherapy can be extended beyond 6 months if clinically indicated. Patients who experience smoking relapse can be considered for second-line therapy.

Treatment for Persistent Smoking or Relapse

For patients who continue to smoke or experience relapse, reevaluate the use of pharmacotherapy and provide additional behavior therapy. The panel recommends continuation of initial pharmacotherapy or switching to the alternate preferred option (combination NRT or varenicline). These regimens should always be paired with continued behavior therapy. Both preferred primary therapy approaches (combination NRT and varenicline) should be tried before proceeding to any of the subsequent pharmacotherapy options.

Subsequent options for pharmacotherapy include combination NRT with bupropion sustained release (SR), or bupropion SR alone (category 2B). Bupropion should be avoided in patients with brain metastases due to increased seizure risk. For further relapse, extended duration of pharmacotherapy can be considered. Additional or more intensive behavior therapy is also an option.

After switching therapy or adjusting the dose of an existing regimen, follow-up should occur within 3 weeks and after 12 weeks of therapy. Smoking status should be re-evaluated. For patients who are smoke-free, the course of pharmacotherapy can be extended as clinically indicated. Additional follow-up at 6 and 12 months after successful quitting is recommended.

Principles of Pharmacotherapy

General

A minimum of 12 weeks of combination NRT or varenicline is recommended for the initial quit attempt. Duration of therapy can be extended to promote continued cessation, but providers should attempt to avoid unnecessarily long treatment duration when possible. Research suggests that longer courses of certain cessation regimens may be associated with higher rates of 7-day point-prevalence abstinence.¹⁸⁵

Follow-up is recommended 2 weeks after starting pharmacotherapy but can be extended to 3 weeks to coordinate with scheduled oncology appointments. For relapse or continued smoking, options include continuation of the initial agent or a switch to the alternative preferred agent. Dose adjustments should be considered as clinically indicated. Attempts at smoking reduction should be tracked. If reduction efforts stall or if complete abstinence seems unlikely, providers should consider an alternative pharmacotherapy regimen.

In most circumstances the side effects related to primary smoking cessation medications are minimal and are considered an acceptable risk compared to smoking. A review of post-marketing case reports on adverse neuropsychiatric effects from smoking cessation medications have generated some safety concerns in the past,¹⁸⁶ but recent large-scale analyses of the data support the safety of these regimens.^{187,188}

Although serious side effects of primary cessation approaches are extremely rare, providers should refer to manufacturer inserts for exhaustive lists of potential side effects and warnings.

Adherence to pharmacotherapy is important to promote optimal outcomes and success, and numerous studies have tested interventions designed to promote and improve medication adherence.¹⁸⁹

Below, data from various clinical trials are discussed. Included in this discussion are findings from a 2013 Cochrane network meta-analysis that included data on pharmacologic interventions across 267 individual studies in 101,804 participants.¹⁹⁰ The authors characterized positive treatment outcome as continuous or prolonged abstinence at least 6 months from the start of smoking cessation therapy. Harm outcomes were measured by the incidence of serious adverse events associated with treatment.

Primary Therapy Options

For patients with cancer, the guidelines recommend primary therapy with either combination NRT or varenicline. If smoking persists or relapse occurs while a patient is on an initial primary therapy regimen, providers should continue therapy with that initial regimen or switch to the alternate primary therapy option. Both preferred primary therapy options should be used before trying any subsequent therapy options. The efficacy and safety data on preferred primary regimens are summarized below.

Combination Nicotine Replacement Therapy

Efficacy

NRT offers an alternative nicotine delivery method and can be used to ameliorate nicotine withdrawal symptoms during cessation attempts. Combination NRT incorporating long-term and fast-acting NRT offers the greatest potential benefits for smokers.^{170,190-192} Cochrane network meta-analysis data published in 2013 support the superiority of combination NRT over single forms of NRT such as nicotine patch (OR, 1.43; 95% CI, 1.08–1.91), nicotine gum (OR, 1.63; 95% CI, 1.21–2.2), and various other forms that collectively include inhaler, lozenge, spray, or tablets (OR, 1.34; 95% CI, 1.0–1.8).¹⁹⁰ All forms of NRT were superior to placebo, but smokers using combination NRT were almost three times as likely to succeed (OR, 2.73; 95% CI, 2.07–3.65).¹⁹⁰ Compared with single forms of NRT, combination NRT using a patch plus short-acting NRT improved the odds of quitting (OR 1.34; 95% CI, 1.18–1.51).^{190,193}

The success of NRT may be contingent on concurrent behavior therapy to support cessation. In a large population study, over-the-counter NRT resulted in similar rates of cessation to those who used no aid. The addition of behavior therapy to NRT increased the odds of success nearly three-fold.¹⁷⁹

Safety

The safety of combination NRT for use in humans has been demonstrated and benefits are considered to outweigh potential risks.¹⁹⁴ Importantly, providers should be aware that blood nicotine levels from NRT, including combination NRT, are significantly less than that from smoking cigarettes.¹⁹⁵⁻¹⁹⁷ In fact, patients commonly underdose when using combination NRT,¹⁸²⁻¹⁸⁴ and although nicotine overdose is possible, it is rare and usually short-lived. Therefore, providers and

smokers should not be dissuaded from using NRT to foster quitting and long-term cessation. Recent reviews of the data suggest that NRT is not linked to increased serious cardiovascular adverse events when used for smoking cessation.¹⁹⁸ While myocardial infarction has rarely been reported in NRT users, there is insufficient evidence that NRT increases the risk of myocardial infarction or cardiovascular disease.^{193,199} Data from large case series have not shown elevated risk with the use of NRT in patients with acute coronary syndromes.^{200,201}

In the past, the safety of NRT has been evaluated in light of the bioactivity of nicotine and evidence that this drug can promote cell growth in certain types of cancer cells.²⁰² Some *in vitro* data suggested that nicotine increased the malignant potential of small cell lung cancer cells²⁰³; induced chemoresistance in models using lung cancer cells¹²³⁻¹²⁵ and nasal epithelial cells¹²⁶; and promoted chemoresistance and metastasis in pancreatic cancer cell and mouse models.¹²⁷ However, other studies suggested no effects of physiological levels of nicotine exposure on tumorigenesis in mouse lung cancer models.^{204,205} Moreover, there is insufficient evidence that NRT causes cancer in humans.²⁰⁴⁻²⁰⁸ Evaluation of data from 3320 participants in the Lung Health Study, which recorded in-study NRT use and smoking exposure, found that NRT was not a significant predictor of lung cancer, while smoking was.²⁰⁷

Varenicline

Efficacy

Varenicline is a non-nicotinic partial agonist of the alpha4beta2 subtype of the nicotinic acetylcholine receptor. Varenicline partially mimics the effects of nicotine in the brain's reward center and competitively inhibits the binding of nicotine from cigarettes.²⁰⁹

Systematic reviews/meta-analyses have identified varenicline as the most effective single pharmacotherapy option for smoking cessation.^{190,210,211} Cochrane network meta-analysis data report that varenicline increases the odds of smoking cessation by almost three-fold compared with placebo (OR, 2.88; 95% CI, 2.40–3.47).¹⁹⁰ Direct comparison of the cumulative data suggest that varenicline was more efficacious than bupropion (OR, 1.59; 95% CI, 1.29–1.96) and single forms of NRT such as nicotine patch, nicotine gum, and other formulations (OR, 1.57; 95% CI, 1.29–1.91).¹⁹⁰ Varenicline appeared to be equally as likely to promote smoking cessation as combined treatment with more than one form of NRT (OR, 1.06; 95% CI, 0.75–1.48), so that both may be offered depending on patient circumstances.¹⁹⁰

Results recently published from the double-blind EAGLES RCT (n = 8144) revealed that varenicline-treated patients achieved higher abstinence rates than patients receiving placebo (OR, 3.61; 95% CI, 3.07–4.24), nicotine patch (OR, 1.68; 95% CI, 1.46–1.93), or bupropion (OR, 1.75; 95% CI, 1.52–2.01).²¹² A recent study investigated the efficacy of varenicline specifically for patients with cancer, revealing 84% retention and 40% abstinence at 12 weeks. Side effect profiles mimicked those observed in the general population, and abstinence improved cognitive function and reduced negative affect over time.²¹³

Varenicline may also be efficacious for smoking reduction. A clinical trial enrolling 1510 individuals revealed that a 24-week course of varenicline effectively promoted smoking cessation in patients who were unwilling to quit but willing to gradually reduce cigarette consumption.²¹⁴ Therefore, this agent provides an alternative for patients who cannot or will not attempt abrupt cessation. A clinical trial in 1236 smokers showed that an additional 12 weeks of varenicline maintenance therapy

helped to sustain continued abstinence in those who successfully quit during initial treatment.²¹⁵

One study examined whether varenicline dose increases would boost treatment efficacy in patients who had a low or no response to standard dosing. A double-blind RCT of 503 smokers found no evidence to suggest that gradual dose titration beyond the standard 2-mg dose (up to a maximum 5 mg/d) lessened frequency of urges and nicotine withdrawal symptoms, or increased cessation rates.²¹⁶ However, nausea and vomiting were increased in the treatment group receiving more than 2 mg/d. Additionally, another RCT showed that varenicline was effective and well-tolerated for retreating patients who had previously received this agent (n = 498).²¹⁷

A recent RCT (n = 1246) examined whether a biomarker of nicotine clearance (nicotine metabolite ratio, NMR) was predictive of nicotine patch versus varenicline efficacy in “slow” versus “normal” metabolizers of nicotine. The findings showed that varenicline was more effective than nicotine patch in normal metabolizers, but varenicline superiority was not observed among slow metabolizers, suggesting the possibility in the future to optimize treatment selection based on this biomarker.²¹⁸

Safety

Varenicline safety has been extensively examined to determine the risk of adverse effects, particularly serious cardiovascular events and neuropsychiatric changes. Initial phase III studies found varenicline to be safe and generally well-tolerated compared with bupropion or placebo; common side effects included nausea, insomnia, and abnormal dreams with rates of approximately 28% to 29%, 14%, and 10% to 13%, respectively.^{219,220}

Concerns regarding neuropsychiatric adverse effects of varenicline have been extensively investigated in smokers with comorbid mental illness.¹⁹⁰ Despite reviews of case reports that raised concern,¹⁸⁶ a 2015 systematic review and meta-analysis of 39 randomized controlled smoking cessation trials identified no evidence to suggest that varenicline increases risk of suicide or suicide attempts, suicidal ideation, depression, or death.¹⁸⁸ Another trial showed that varenicline increased smoking cessation rates without exacerbating anxiety and depression symptoms in adults with stably treated current or past depression.²²¹ Results were recently published from a large double-blind RCT (EAGLES trial) that enrolled 2 cohorts: individuals with psychiatric disorders (n = 4116) and those without psychiatric disorders (n = 4028). No significant increase in neuropsychiatric events was observed for varenicline relative to nicotine patch or placebo. Varenicline was associated with significantly higher abstinence rates than bupropion plus nicotine patch, as well as placebo.²¹²

Cardiovascular risks have also been examined. Importantly, recent systematic reviews and meta-analyses of RCT data have not identified a significant link between varenicline and increased risk of serious cardiovascular adverse events.^{190,198,222,223} However, the cardiovascular safety of varenicline has remained a topic of interest and concern.²²⁴⁻²²⁶

In a 2015 retrospective review of 164,766 individuals who received pharmacotherapy for smoking cessation (varenicline, n = 51,450; NRT, n = 106,759; bupropion, n = 6557), neither varenicline nor bupropion posed an elevated risk of cardiovascular or neuropsychiatric (depression, self-harm) events compared with NRT.²²⁷ Based on the current evidence base for safety risks, the panel considers varenicline to be safe and to have a favorable risk/benefit ratio for use in patients with cancer who smoke.

Although rare, elevated seizure risk is a concern with varenicline therapy.^{228,229} In patients with brain metastases who have a history or elevated risk of seizure, varenicline should be avoided.

Subsequent Therapy Options

Recommended subsequent therapy options in these guidelines include combination NRT with bupropion SR or bupropion SR alone (category 2B). Currently, other regimens are not recommended in this treatment setting. However, the panel acknowledges ongoing evaluation of alternative regimens (eg, varenicline plus combination NRT; varenicline plus bupropion, nortriptyline, or clonidine). The panel regularly reviews the evidence base for alternative regimens when updating these guidelines. The data for various regimens are summarized below.

Recommended Regimens

Bupropion + NRT

A large trial in the United Kingdom (n = 1071) examined the efficacy of NRT alone, bupropion alone, and NRT plus bupropion.²³⁰ All participants received 7 weeks of behavior therapy support in addition to the pharmacologic interventions. Abstinence rates at 6-month follow-up ranged from 24.2% to 27.9% and did not differ significantly between cohorts. Several unwanted side effects were more common with bupropion than NRT (eg, disturbed sleep, dry mouth, headaches, nausea), and side effects of combination therapy were not significantly different versus bupropion alone. Five serious adverse events occurred in the bupropion group, including allergic reaction (n = 3), neuropsychiatric symptoms (n = 1), and chest pain (n = 1). A trend toward improved efficacy of bupropion in patients with a history of depression was noted ($\chi^2 = 2.86$, $P = .091$).

A double-blind RCT compared bupropion + NRT, bupropion alone, nicotine patch alone, and placebo in 893 individuals who smoked at least 15 cigarettes per day. At 12 months, the highest abstinence rates were observed for the bupropion + NRT group (35.5%) and bupropion only group (30.3%), although these groups did not differ significantly.²³¹ A smaller RCT studying the addition of bupropion to combination NRT and behavior therapy in patients with schizophrenia suggested that combination pharmacotherapy promoted smoking reduction and cessation, but also demonstrated a high relapse rate after discontinuation of treatment.²³² A 2014 meta-analysis of 12 trials examining this combination revealed a nonsignificant trend in improved cessation with the addition of NRT to bupropion.²³³

Bupropion

Bupropion was first approved to treat depression but its efficacy as a cessation aid also became apparent. In addition to its effects on the dopaminergic and adrenergic systems, this agent also acts as an inhibitor of nicotinic acetylcholinergic receptors. A 2014 Cochrane review of 44 trials examined bupropion efficacy, revealing an RR of 1.62 (95% CI, 1.49–1.76).²³³ Recent results from the EAGLES trial (n = 8144) revealed that patients receiving bupropion achieved superior abstinence rates compared with placebo (OR, 2.07; 95% CI, 1.75–2.45).²¹² Efficacy was similar to nicotine patch but less than that for varenicline. Some evidence suggests that bupropion may be particularly beneficial as a smoking cessation agent for persons with depression.^{230,234} Additionally, longer duration of bupropion treatment may help to prevent relapse in those who have successfully quit.²³⁵

Bupropion reduces the seizure threshold and meta-analyses of trial data have found a 0.1% seizure risk among those receiving the drug for smoking cessation.²³³ In patients with brain metastases who have a history or elevated risk of seizure, bupropion should be avoided.

Neuropsychiatric effects have also been identified as a safety concern with bupropion, although to a lesser extent than varenicline.¹⁸⁶ However, recent systematic reviews of the data have found that serious neuropsychiatric adverse events were rarely associated with bupropion prescribed for smoking cessation, including studies of bupropion in patients with mental illness.^{190,236} In the EAGLES trial, no significant increase in neuropsychiatric events was observed for bupropion relative to nicotine patch or placebo.²¹²

Similarly, regarding risk of serious adverse cardiovascular effects, recent meta-analyses do not show elevated risk as a result of bupropion use for smoking cessation.^{190,198,233}

Other Regimens

Several other pharmacotherapy regimens for smoking cessation have been studied in clinical trials but are not recommended by the panel at this time based on the existing data. Data from these studies are summarized below for informational purposes.

Varenicline + NRT

A study in 435 smokers found that the addition of nicotine patch to varenicline therapy significantly increased the cessation rates at the end of treatment (12 weeks), at 24 weeks, and at 6-month follow-up.²³⁷ No significant differences were noted for side effect incidence between varenicline/NRT and varenicline/placebo with the exception of skin reactions, which were increased with combination therapy (14.4% vs. 7.8%; $P = .03$). However, one RCT of 341 smokers did not find enhanced cessation rates at 12- and 24-week follow-up among individuals receiving a combination of varenicline and nicotine patch, versus varenicline alone.²³⁸ The addition of nicotine patch to varenicline did not cause significant changes in side effect profiles. Similarly, a trial in 117 participants did not find evidence that the addition of NRT to

varenicline increased abstinence rates at 1, 4, or 12 weeks after the targeted quit date, and no between-group differences in adverse effects were found.²³⁹

Varenicline + Bupropion

In an RCT of smokers who demonstrated an inadequate response to front-line nicotine patch treatment (n = 222), combination therapy with varenicline and bupropion appeared to be more efficacious than varenicline alone as a second-line therapy option.²⁴⁰ This observation was more pronounced among male smokers and those with a high level of nicotine dependency. Although no significant differences in side effects were observed between varenicline and bupropion versus varenicline alone, dose reductions were required for 11.5% and 24.8% of patients, respectively. Common side effects were vivid dreams, change in taste perception, thirst, insomnia, and irritability. Another study of varenicline + bupropion therapy versus varenicline alone (n = 316) demonstrated that combination therapy increased prolonged abstinence but did not affect 7-day point prevalence at 12 and 26 weeks follow-up, and no significant differences were observed between the groups at 52 weeks.²⁴¹ In this study, anxiety (7.2% vs. 3.1%; $P = .04$) and depressive symptoms (3.6% vs. 0.8%; $P = .03$) occurred more frequently in patients receiving combination therapy versus varenicline alone.

Nortriptyline and Clonidine

Studies have also suggested some efficacy of off-label use of nortriptyline, a tricyclic antidepressant, as well as the antihypertensive agent clonidine.

A Cochrane network review identified 6 trials comparing nortriptyline with placebo, finding a pooled RR of 2.03 (95% CI, 1.48–2.78).^{102,133}

However, as an adjunct to NRT, clear-cut benefits were not observed.^{190,242}

Clonidine is recommended as a third-line smoking cessation option. Although several studies have produced data in favor of clonidine as a cessation aid versus placebo, not all study data reveal a statistically significant effect. Additionally, clonidine's benefits can be counteracted by dose-dependent increases in drug side effects. A 2013 Cochrane network review of data from 6 studies resulted in a pooled RR of 1.63 (95% CI, 1.22–2.18).¹⁰²

Principles of Behavior Therapy

General Principles

The guidelines provide the following guiding principles on behavior therapy, which have been developed in consideration of the existing evidence base, clinical practice guidelines, and expert consensus.^{180,181,194}

The panel recommends a combination of behavior therapy with pharmacotherapy for best outcomes. In fact, studies suggest that counseling for smoking cessation may enhance patient satisfaction.^{15,16} A 2012 systematic review of 41 studies provided support for the efficacy of this approach.¹⁸⁰ The “real world effectiveness” of adding a behavior therapy component to smoking cessation therapy was further supported by a large population study published in 2014.¹⁷⁹ Additionally, a 2016 meta-analysis of data from 1239 patients with head and neck cancer showed improved smoking cessation rates with the addition of counseling to usual care (NRT).²⁴³

Behavior therapy may enhance motivation and support optimal medication strategies and adherence to pharmacotherapy. When possible, therapy should be provided by a tobacco treatment specialist



or dedicated staff member (ie, nurse, medical assistant, health educator) with training in motivational and behavior strategies for smoking cessation.

As a general principle, more intensive behavior therapy is preferred over brief advice or counseling.¹⁸¹ The evidence supports a measurable dose-response effect of behavior therapy with more numerous and/or longer sessions delivering improved outcomes. The panel defines intensive behavioral therapy as at least 4 sessions within 12 weeks (in person; group or individual) lasting at least 10 minutes but typically 30 minutes or longer. As patients progress through multiple lines of pharmacotherapy, behavior therapy should be progressively intensified with referral to specialty care (eg, psychiatrist, psychologist) as indicated. Studies have also demonstrated additional benefit for relapse prevention of extending behavioral therapy for six months or more.²⁴⁴⁻²⁴⁶ Importantly, if intensive therapy is not feasible, brief counseling should still be given. Studies have demonstrated a small but significant benefit of counseling lasting only a few minutes.⁴¹⁻⁴⁴

The most successful behavior therapy strategies employ practical counseling, which addresses problem solving and skills training, as well as social support and MI (see section on *Motivational Interviewing* below) as elements of the treatment plan.^{159,194} Optimally, behavior therapy plans should take into account a patient's nicotine dependence levels, previous quit attempts, and cessation aids utilized. In doing so, patients can be equipped with tailored strategies to cope with nicotine withdrawal symptoms, environmental smoking triggers, and stressful situations. For instance, the addition of a cognitive behavior therapy program designed to improve stress management improved cessation rates over controls receiving standard smoking cessation therapy.²⁴⁷

Providers should prepare patients for nicotine withdrawal symptoms and cravings, which typically peak at several days to 2 weeks post-cessation before gradually subsiding.²⁴⁸⁻²⁵⁰

A number of modalities can be employed to deliver behavior therapy to patients. Counseling can take place in a variety of settings such as in person, remotely by telephone,⁴⁵ or through web-based interventions.²⁵¹ Effective in-person counseling can occur as an individual session or in the group therapy setting.^{252,253} Additionally, print materials²⁵⁴ and mobile telephone “apps”²⁵⁵⁻²⁵⁷ can be used to deliver behavior therapy. However, providers should be aware that media-based behavioral interventions, particularly those using mobile telephones, may vary in the degree to which they comply with clinical practice guidelines.²⁵⁸

A recent study investigated preferences for the provision of smoking cessation information among Canadian patients with cancer. Patients most often preferred print materials (45%), followed by telephone support (39%), speaking with a clinician (29%), website-based information (15%), and support groups (11%). Younger patients (≤45 years) were more likely to prefer cessation advice via telephone, while older patients preferred print materials.²⁵⁹ Selection of a particular modality or modalities should be guided by patient preference, medical history, and resource availability.

For patients who are unable to quit, referral to a smoking cessation clinic is encouraged when available. If specialized resources are limited, effective behavior counseling can still be provided. For instance, brief counseling by providers has been shown to generate a small but important increase in quit rates.⁴¹⁻⁴³ Additionally, quitlines can provide essential behavioral support in the absence of in-person counseling resources.⁴⁵ For instance, the addition of combination NRT to quitline counseling improved cessation outcomes.²⁶⁰

Tailoring Behavior Therapy for Patients with Cancer

As resources allow, specialized treatment centers should provide tailored smoking cessation therapy programs that address the unique needs of patients with cancer, or refer to external resources (eg, quitlines) that provide such specialized services. For patients in active cancer treatment, behavior therapy can be provided during scheduled oncology visits to obviate the need for additional appointments. Beneficial services might include individual and group therapy focusing on the challenges specific to cancer treatment and survival, which would ideally be provided by clinicians experienced in working with patients with cancer. A recent study suggested age-based differences in preferences for smoking cessation resources.²⁵⁹

The prevalence of mental disorders or serious emotional issues in patients with cancer is high, with several large studies reporting rates between 30% and 40%.²⁶¹⁻²⁶³ The high rates of anxiety, depression, and stress can present a significant challenge for patients with cancer who attempt to quit smoking in the face of these common smoking/relapse triggers. Patients with cancer, particularly those experiencing psychiatric comorbidity, may benefit significantly from behavior therapy programs tailored to manage cancer-related issues that predispose patients to relapse. Referral to specialized smoking cessation programs may be necessary so that these patients have access to staff trained to treat comorbid substance dependence and mental health disorders.

Motivational Enhancement

All cancer patients and survivors should be encouraged to quit. Strategies to enhance motivation to quit are beneficial for all patients, including those who are currently ambivalent or unwilling to quit. Motivational interviewing is one evidence-based approach to foster motivation to quit in which a clinician offers empathy as the patient

explores ambivalence regarding quitting smoking. Clinicians reflect, validate, and summarize patient concerns and help patients identify discrepancies between smoking and core values/goals (eg, health, parenting) and support patient confidence regarding quitting.^{29,158,159}

A 2015 Cochrane database review of 28 studies examined the efficacy of MI for smoking cessation, revealing a modest but significant increase in chance of quitting with MI versus brief advice or usual care.²⁶⁴ MI by a primary care physician appeared to be somewhat more successful than that administered by counselors, although both were effective. Notably, one-time short MI sessions of less than 20 minutes had demonstrated efficacy.²⁶⁴ A recent systematic review summarized the evidence to support MI for behavioral change, including smoking cessation, in patients with cancer.²⁶⁵

In order to promote willingness to quit smoking, the US Preventive Services Task Force (USPSTF) recommends a model of MI that employs the “5 R’s” of the personal Relevance of quitting; personal Risks of continuing smoking; personal Rewards of quitting; identifying Roadblocks to quitting; and Repeating the message at every contact.¹⁹⁴ This model encourages that motivational information be relevant to the individual patient, and that clinicians and patients work together to identify personalized risks of smoking and potential rewards of cessation. By having the patient identify perceived roadblocks to quitting, providers can suggest tailored treatments to address patient-reported concerns. Finally, this model recommends repetition of MI at each patient visit, coupled with reminders that repeated quit attempts may be necessary to achieve long-term cessation.

Alternative Treatment Approaches

The panel has reviewed the available evidence for alternative smoking cessation treatment approaches. Continue to provide motivational and

behavioral support to all patients during quit attempts, regardless of what smoking cessation methods are being used, including e-cigarettes. Particular attention has been paid to the discussion of e-cigarettes for smoking cessation given increasing popularity and widespread use. Limited data are available on the safety and efficacy of these approaches, specifically for patients with cancer; data have been drawn primarily from studies in the general population.

The panel has found insufficient evidence to support the use of alternative therapies alone or in combination with standard smoking cessation methods, and use of alternative therapies is not recommended. The guidelines recommend that patients use evidence-based cessation methods to avoid any delay in achieving smoking abstinence. Smoking slips and relapse are common, and prior unsuccessful quit attempts with conventional therapies do not justify the use of unproven alternative cessation methods. When discussing alternative therapies, providers should counsel patients on potential interactions with evidence-based cessation methods and/or cancer treatments.

Electronic Cigarettes/Electronic Nicotine Delivery Systems

The popularity of electronic cigarettes, “e-cigarettes,” and their various derivatives is a recent phenomenon, and, as such, the available literature is new and relatively limited, particularly within specific subpopulations such as patients with cancer. Electronic nicotine delivery systems (ENDS) are not FDA-approved smoking cessation devices. At the present time, the panel does not recommend use of e-cigarettes, and instead known effective methods for smoking cessation should be offered. Below, we discuss the current data and expert opinions on e-cigarettes for smoking cessation.

Several health care organizations have released similar policy statements concerning ENDS, highlighting the urgent need for research on the safety of these devices and efficacy as a cessation aid. The American Heart Association, AACR, and ASCO recognize the potential for ENDS to alter existing smoking behaviors, as well as the lack of definitive data regarding associated benefits and harms.^{266,267} Experts in the field generally acknowledge that ENDS may offer an attractive approach for smoking reduction and/or cessation in certain populations. However, these policy statements also highlight the unknown potential for ENDS to affect nicotine addiction, combustible tobacco product use, and renormalization of smoking behaviors. In the September 2015 Final Recommendation Summary, the USPSTF concluded “that the current evidence is insufficient to recommend ENDS for tobacco cessation. The USPSTF recommends that clinicians direct patients who smoke tobacco to other cessation interventions with established effectiveness and safety”.²⁶⁸ Currently, provider education and training on e-cigarette use may be inadequate, and clinicians have reported low confidence in their ability to provide patient counseling on this matter.²⁶⁹

One study examined e-cigarette use in 1074 patients with cancer who enrolled in a tobacco treatment program at a comprehensive cancer center.²⁷⁰ The study revealed a marked increase in e-cigarette use from 10.6% to 38.5% between 2012 and 2013. E-cigarette users, most often patients with thoracic or head and neck cancers, were more nicotine dependent and had greater numbers of prior quit attempts. At follow-up (6–12 months after intake), e-cigarette users were no more likely to have quit than non-users (OR, 1.0; 95% CI, 0.5–1.7), calling into question the potential benefits of e-cigarettes as a cessation agent for patients with cancer. In a cross-sectional analysis of cancer survivors in the United States (n = 2695 excluding non-melanoma skin cancers), e-cigarette use was highest among current cigarettes smokers, compared

with former or never cigarette smokers.²⁷¹ Collectively, these studies highlight the importance of addressing e-cigarette usage by patients with cancer and cancer survivors.

High-quality data on e-cigarette use for smoking cessation, including head-to-head comparisons of e-cigarettes with evidence-based therapies, are extremely limited. In the largest RCT to date, 657 individuals were randomized to receive nicotine e-cigarettes, placebo e-cigarettes, or nicotine patch. Abstinence rates were unexpectedly low across all groups, with no statistically significant differences in biochemically verified smoking abstinence between treatment groups at 6 months.²⁷² Systematic reviews have summarized the data from the general population to determine the potential efficacy of e-cigarettes as a smoking cessation aid. Conclusions have varied, likely due to the limited overall pool of data and heterogeneous study measures.

Recent data suggest a detrimental impact of e-cigarette use on smoking cessation. In a comprehensive meta-analysis of 20 controlled studies (2 trials, 15 cohort studies, and 3 cross-sectional studies), individuals using e-cigarettes were 28% less likely to achieve smoking cessation (OR, 0.72; 95% CI, 0.57–0.91).²⁷³ Sensitivity analyses revealed no impact of quit intention and other study variables. Similarly, e-cigarette use did not decrease cigarette smoking in a cross-sectional study in 106 patients with head and neck cancers seeking to quit. Non-users of e-cigarettes had a significantly greater rate of cessation compared with e-cigarette users (72% vs. 39%; $P = .0057$).²⁷⁴

However, some earlier studies suggested a potential benefit of e-cigarettes for smoking cessation. In one meta-analysis, findings suggested that more individuals reduced cigarette consumption with nicotine e-cigarette vs. placebo (RR, 1.31; 95% CI, 1.02–1.68), and one study suggested that nicotine e-cigarettes improved reduction over

nicotine patch (RR, 1.41; 95% CI, 1.20–1.670).²⁷⁵ Across all 13 studies examined, no serious adverse events were reported.²⁷⁵ Similarly, a 2015 systematic review and meta-analysis of data from 1242 participants suggested that nicotine-containing e-cigarettes were more effective cessation aids than non-nicotine-containing e-cigarettes (RR, 2.29; 95% CI, 1.05–4.97).²⁷⁶ E-cigarette use over a minimum of 6 months was associated with an 18% reported smoking cessation rate (effect size, 0.20; 95% CI, 0.11–0.28), and e-cigarette use was also associated with smoking reduction.²⁷⁶ A large cross-sectional study of 5863 adults in the United Kingdom assessed the “real-world effectiveness” of e-cigarettes for smoking cessation compared to NRT and unaided quitting, revealing that e-cigarette users were more likely to report abstinence compared with the other cohorts (e-cigarettes vs. NRT: OR, 2.23; 95% CI, 1.70–2.93; e-cigarettes vs. no aid OR 1.38; 95% CI, 1.08–1.76).²⁷⁷ These observations persisted when adjusting for measures of nicotine dependence across the cohorts.

Other Alternative Approaches

Very limited data exist to support exercise-based interventions; small study size, inadequate controls, and insufficient exercise intensity limit the ability to make conclusions based on the existing evidence.²⁷⁸ Sufficient efficacy data are also lacking to support the use of alternative therapies such as acupuncture, hypnosis, and nutritional supplements. A 2014 systematic review of the data on acupuncture, acupressure, and laser therapy revealed no consistent, bias-free evidence to support these methods for smoking cessation, although pooled evidence was suggestive of possible short-term benefits.²⁷⁹ Acupuncture was less effective than NRT and there was no evidence to support electrostimulation for smoking cessation. Similarly, systematic reviews of the data on hypnosis for smoking cessation revealed inadequate high-quality evidence to support this approach.^{280,281} Claims of efficacy

data for hypnosis from several studies were not substantiated by the review of RCT data. Controlled studies are needed to provide higher quality evidence on these interventions both in the general population and among patients with cancer.





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Discussion
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