FLORIDA CANCER SPECIALISTS & Research Institute

TOP ARTICLES OF THE MONTH

SEPTEMBER 2021 | Lucio N. Gordan, MD

1. Esophageal Carcinoma: ASCO Treatment of Locally Advanced Esophageal Carcinoma Guideline Rapid Recommendation Update

Manish A. Shah, MD; Erin B. Kennedy, MHSc; Daniel V. Catenacci, MD; Dana C. Deighton; Karyn A. Goodman, MD; Narinder K. Malhotra, MD; Christopher Willett, MD; Brendon Stiles, MD; Prateek Sharma, MD; Laura Tang, MD, PhD; Bas P. L. Wijnhoven, MD, PhD; and Wayne L. Hofstetter, MD

**M.A.S. and W.L.H. were Expert Panel cochairs.*

ASCO Rapid Recommendations Updates highlight revisions to select ASCO guideline recommendations as a response to the emergence of new and practice-changing data. The rapid updates are supported by an evidence review and follow the guideline development processes outlined in the ASCO Guideline Methodology Manual. The goal of these articles is to disseminate updated recommendations, in a timely manner, to better inform health practitioners and the public on the best available cancer care options.

In 2020, ASCO published a guideline on the management of locally advanced esophageal cancer.[1] The CheckMate 577 double-blind, placebo-controlled, phase III randomized controlled trial (RCT) was recently reported, evaluating the efficacy of the addition of the checkpoint inhibitor nivolumab following neoadjuvant chemoradiotherapy (CRT) and surgery in patients with stage II/III esophageal carcinoma with residual disease (ie, patients who had viable disease in the surgical resection specimen after receiving CRT).[2] The CheckMate 577 results provided a strong signal indicating the need to update the 2020 guideline recommendations.

A targeted electronic literature search was conducted to identify any additional phase III RCTs of treatment options in this patient population. No additional RCTs were identified. The original guideline Expert Panel was reconvened to review new evidence from CheckMate 577 and to review and approve the revised recommendation.

The RCT by Kelly et al[2] included 794 patients with esophageal or gastroesophageal junction adenocarcinoma (71%) or esophageal squamous cell carcinoma (29%) and residual pathological disease after neoadjuvant CRT and an R0 resection. More than 50% of patients had lymph node–positive disease. The primary outcome, disease-free survival (DFS), was significantly improved for patients receiving neoadjuvant CRT + surgery and adjuvant nivolumab compared to CRT + surgery and adjuvant placebo (hazard ratio: 0.69; 96.4% CI, 0.56 to 0.86; $P < .001$). Treatment-related grade 3-4 adverse events were experienced by 13% versus 6% in the nivolumab and placebo groups, respectively (relative risk: 2.31; 95% CI, 1.35 to 3.96; $P = .002$). Using the GRADE methodology,[3] study quality was downgraded from high to moderate because the number of events needed to report on secondary outcome overall survival has not yet been achieved. The DFS results were significant across both adenocarcinoma and squamous cell carcinoma subgroups.

Prior to the publication of the CheckMate 577 data, the ASCO 2020 guideline for locally advanced esophageal cancer did not include recommendations for further treatment of patients with residual disease following resection and CRT. The previous standard of care for this patient population was surveillance.

Following neoadjuvant CRT and surgery, nivolumab should be offered to patients with locally advanced esophageal carcinoma with Eastern Cooperative Oncology Group status 0-1 who did not experience a pathological complete response (ie, with residual disease of at least ypT1 or ypN1 in resected specimens; Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

QUALIFYING STATEMENTS

- Data are not available to support any recommendation for nivolumab following treatment with perioperative chemotherapy.
- A post hoc analysis showed an hazard ratio for DFS of 0.62 (95% CI, 0.46 to 0.83; median DFS 29.4 v 10.2 months) in the subgroup of patients with programmed death-ligand 1 (PD-L1) combined positive score (CPS) of at least 5 (n = 371) and 0.89 (95% CI, 0.65 to 1.22; median DFS 16.3 v 11.1 months) in the subgroup of patients with PD-L1 CPS of < 5 (n = 295). This exploratory analysis suggests that future studies may define biomarkers, such as PD-L1 CPS, and/or a subgroup that will benefit from adjuvant nivolumab.

---

2. Adjuvant PARP Inhibitors in Patients With High-Risk Early-Stage HER2-Negative Breast Cancer and Germline BRCA Mutations: ASCO Hereditary Breast Cancer Guideline Rapid Recommendation Update

Nadine M. Tung , MD; Dana Zakalik , MD; and Mark R. Somerfield , PhD; for the Hereditary Breast Cancer Guideline Expert Panel

**N.M.T. and D.Z. were Expert Panel cochairs.*

ASCO Rapid Recommendations Updates highlight revisions to select ASCO guideline recommendations as a response to the emergence of new and practice-changing data. The rapid updates are supported by an evidence review and follow the guideline development processes outlined in the ASCO Guideline Methodology Manual. The goal of these articles is to disseminate updated recommendations, in a timely manner, to better inform health practitioners and the public on the best available cancer care options.

In 2020, ASCO published a guideline on the management of hereditary breast cancer.[1] On June 3, 2021, the OlympiA phase III, double-blind, randomized trial reported on the efficacy of adjuvant poly(ADP–ribose) polymerase (PARP) inhibitor therapy with olaparib in patients with early-stage, human epidermal growth factor receptor 2 (*HER2*)–negative breast cancer with high risk of recurrence and germline BRCA1 or BRCA2 pathogenic or likely pathogenic variants.[2] A significant improvement in invasive and distant disease-free survival constituted a strong signal for an update of the 2020 ASCO-ASTRO-SSO guideline recommendation focused specifically on the role of PARP inhibitors in patients with early-stage, *HER2*-negative breast cancer and germline BRCA mutations.

A targeted literature search was conducted to identify phase III clinical trials pertaining to the recommendation on PARP inhibitors in this patient population. No additional randomized trials were identified. The original Expert Panel was reconvened to review the evidence from OlympiA and to approve the updated recommendation.

Tutt et al[2] reported that, compared with placebo, one year of olaparib following the completion of local treatment and (neo)adjuvant chemotherapy was associated with significantly longer survival free of invasive or distant disease (interim analysis with a median follow-up of 2.5 years). Patients had completed at least six cycles of neoadjuvant or adjuvant chemotherapy; 95% of patients in the trial received anthracycline- and taxane-based chemotherapy. In the olaparib group, the 3-year invasive disease-free survival was 85.9% versus 77.1% in the placebo group (hazard ratio, 0.58; 99.5% CI, 0.41 to 0.82; P < .001). In the olaparib group, the 3-year distant disease-free survival was 87.5% versus 80.4% in the placebo group (hazard ratio, 0.57; 99.5% CI, 0.39 to 0.83; P < .001). Anemia was the only grade 3 adverse event reported in > 5% of patients. In the olaparib group, 8.7% of patients had grade ≥ 3 anemia versus 0.3% of patients in the placebo group. More patients in the olaparib group had at least one blood transfusion with 5.8% versus 0.9% in the placebo group. The occurrence of serious adverse events, including myelodysplastic syndrome and acute leukemia, was not more frequent in the olaparib arm versus placebo.

2020 RECOMMENDATION

Before the publication of the OlympiA data,[2] the management of hereditary breast cancer joint Panel published this practice recommendation in 2020: For germline BRCA mutation carriers, there are insufficient data at this time to recommend a PARP inhibitor for patients with nonmetastatic breast cancer.

2021 UPDATED RECOMMENDATION

The updated recommendation for June 2021 is that for patients with early-stage, *HER2*-negative breast cancer with high risk of recurrence and germline BRCA1 or BRCA2 pathogenic or likely pathogenic variants, one year of adjuvant olaparib should be offered after completion of (neo)adjuvant chemotherapy and local treatment, including radiation. For those who had surgery first, 1 year of adjuvant olaparib should be offered for patients with triple-negative breast cancer and tumor size > 2 cm or any involved axillary nodes. For those with hormone receptor–positive disease, 1 year of adjuvant olaparib should be offered to those with at least four involved axillary lymph nodes. For patients who had neoadjuvant chemotherapy, 1 year of adjuvant olaparib should be offered to patients with triple-negative breast cancer and any residual cancer; for patients with hormone receptor–positive disease, 1 year of adjuvant olaparib should be offered to patients with residual disease and a clinical stage, pathologic stage, estrogen receptor, and tumor grade score ≥ 3.

Although the 3-year estimated overall survival was greater with olaparib, the difference was not statistically significant at the time of this interim analysis at a 2.5-year median follow-up. Of note, postneoadjuvant capecitabine was not permitted in the OlympiA trial because this therapy was not the standard of care when the trial was designed. Thus, the trial cannot inform the relative efficacy of olaparib as compared with capecitabine in this context. Safety and tolerability in OlympiA were manageable, and no significant problems with quality of life (global measurement) were noted at the interim analysis. Further follow-up is needed for myelodysplastic syndrome and acute myelogenous leukemia given that PARP inhibitors are DNA-interacting drugs and have the potential to induce hematologic malignancies. Finally, OlympiA did not assess the effect of olaparib as adjuvant therapy in any hereditary forms of breast cancer other than that associated with germline BRCA1 or BRCA2 mutations or assess benefit in patients who lack the high-risk clinical features required for eligibility in this trial.

---

3. Radiation and Androgen Deprivation Therapy With or Without Docetaxel in the Management of Nonmetastatic Unfavorable-Risk Prostate Cancer: A Prospective Randomized Trial

Anthony V. D'Amico, MD, PhD; Wanling Xie, MS; Elizabeth McMahon, RN; Marian Loffredo, RN, OCN; Shana Medeiros; David Joseph, MD; Jim Denham, MD; Parvesh Kumar, MD; Glenn Bubley, MD; Molly Sullivan, MD; Richard Hellwig, MD; Juan Carlos Vera, MD; Rolf Freter, MD, PhD; W. Jeffrey Baker, MD; Jeffrey Y. Wong, MD; Andrew A. Renshaw, MD; and Philip W. Kantoff, MD

PURPOSE

Although docetaxel is not recommended when managing men with unfavorable-risk prostate cancer (PC) given negative or inconclusive results from previous randomized trials, unstudied benefits may exist.

METHODS

Between September 21, 2005, and January 13, 2015, we randomly assigned 350 men 1:1 with T1c-4N0M0 unfavorable-risk PC to receive radiation therapy (RT) and androgen deprivation therapy (ADT) plus docetaxel (60 mg/m2 once every 3 weeks for three cycles before RT and 20 mg/m2 once weekly during RT) versus ADT + RT. We evaluated the treatment effect of adding docetaxel to ADT + RT on the primary end point of overall survival

(OS) and the incidence of RT-induced cancers and explored whether the impact of the treatment effect on OS differed within prostate-specific antigen (PSA) subgroups (< 4, > 20 v 4-20 ng/mL) using the interaction test for heterogeneity adjusted for age and PC prognostic factors.

RESULTS

After a median follow-up of 10.2 years, 89 men died (25.43%); of these, 42 from PC (47.19%). Although OS was not significantly increased in the docetaxel arm (the restricted mean survival time over 10 years was 9.11 v 8.82 years; P = .22), significantly fewer RT-induced cancers were observed (10-year estimates: 0.61% v 4.90%; age-adjusted hazard ratio of 0.13; 95% CI, 0.02 to 0.97; P = .046). The treatment effect of adding docetaxel to ADT + RT on OS significantly differed in men with a PSA < 4 ng/mL versus 4-20 ng/mL (adjusted hazard ratio: 0.27 and 1.51, respectively) because of less PC-specific mortality on the docetaxel arm (0.00% v 28.57%) among men with PSA < 4 ng/mL.

CONCLUSION

Adding docetaxel to ADT + RT did not prolong OS in men with unfavorable-risk PC, but decreased RT-induced cancer incidence, and may prolong OS in the subgroup of men with a PSA < 4 ng/mL by reducing PC-specific mortality.

---

4. Efficacy of venetoclax plus rituximab for relapsed CLL: 5-year follow-up of continuous or limited- duration therapy

Shuo Ma, John F Seymour, Danielle M Brander, Thomas J Kipps, Michael Y Choi, Mary Ann Anderson , Kathryn Humphrey, Abdullah Al Masud, John Pesko, Ruby Nandam, Ahmed Hamed Salem, Brenda Chyla, Jennifer Arzt, Amanda Jacobson, Su Young Kim, Andrew W Roberts

ABSTRACT

We report long-term follow-up of the phase 1b study of venetoclax and rituximab (VenR) in patients with relapsed chronic lymphocytic leukemia (CLL), including outcomes with continuous or limited-duration therapy. Patients received venetoclax daily (200-600 mg) and rituximab over 6 months and then received venetoclax monotherapy. Patients achieving complete response (CR), CR with incomplete marrow recovery (CRi), or undetectable minimal residual disease (uMRD) assessed by flow cytometry ($<10^{-4}$ cutoff) were allowed, but not required, to discontinue therapy, while remaining in the study and could be retreated with VenR upon progression.

Medi

an follow-up for all patients (N = 49) was 5.3 years. Five-year rates (95% CI) for overall survival, progression-free survival, and duration of response were 86% (72-94), 56% (40-70), and 58% (40-73), respectively. Of the 33 deep responders (CR/CRi or uMRD), 14 remained on venetoclax monotherapy (continuous therapy), and 19 stopped venetoclax therapy (limited-duration therapy) after a median of 1.4 years.

Five-year estimates of ongoing response were similar between continuous (71%; 95% CI, 39-88) or limited-duration therapy (79% [49-93]). Six of 19 patients in the latter group had subsequent disease progression, all >2 years off venetoclax (range, 2.1-6.4). Four patients were retreated with VenR, with partial responses observed in the 3 evaluable to date. VenR induced deep responses that were highly durable with either continuous or limited-duration therapy. Retreatment with VenR induced responses in patients with CLL progression after discontinuing therapy.

Continuous exposure to venetoclax in deep responders does not appear to provide incremental benefit.

5. A predictive algorithm using clinical and laboratory parameters may assist in ruling out and in diagnosing MDS

Howard S Oster, Simon Crouch, Alexandra Smith, Ge Yu, Bander Abu Shrkihe, Shoham Baruch, Albert Kolomansky, Jonathan Ben-Ezra, Shachar Naor, Pierre Fenaux, Argiris Symeonidis, Reinhard Stauder, Jaroslav Cermak, Guillermo Sanz, Eva Hellström-Lindberg, Luca Malcovati, Saskia Langemeijer, Ulrich Germing, Mette Skov Holm, Krzysztof Madry, Agnes Guerci-Bresler, Dominic Culligan, Laurence Sanhes, Juliet Mills, Ioannis Kotsianidis, Corine van Marrewijk, David Bowen, Theo de Witte, Moshe Mittelman

KEY POINTS

- A BM examination is the gold standard for the diagnosis of MDS, but it is invasive and subjective.
- A predictive algorithm/app using data of 10 readily available parameters from 1004 subjects was developed to help diagnose/rule out MDS.

ABSTRACT

We present a noninvasive Web-based app to help exclude or diagnose myelodysplastic syndrome (MDS), a bone marrow (BM) disorder with cytopenias and leukemic risk, diagnosed by BM examination. A sample of 502 MDS patients from the European MDS (EUMDS) registry (n > 2600) was combined with 502 controls (all BM proven). Gradient-boosted models (GBMs) were used to predict/exclude MDS using demographic, clinical, and laboratory variables. Area under the receiver operating characteristic curve (AUC), sensitivity, and specificity were used to evaluate the models, and performance was validated using 100 times fivefold cross-validation. Model stability was assessed by repeating its fit using different randomly chosen groups of 502 EUMDS cases. AUC was 0.96 (95% confidence interval, 0.95-0.97). MDS is predicted/excluded accurately in 86% of patients with unexplained anemia. A GBM score (range, 0-1) of less than 0.68 (GBM < 0.68) resulted in a negative predictive value of 0.94, that is, MDS was excluded. GBM ≥ 0.82 provided a positive predictive value of 0.88, that is, MDS. The diagnosis of the remaining patients (0.68 ≤ GBM < 0.82) is indeterminate. The discriminating variables: age, sex, hemoglobin, white blood cells, platelets, mean corpuscular volume, neutrophils, monocytes, glucose, and creatinine. A Web-based app was developed; physicians could use it to exclude or predict MDS noninvasively in most patients without a BM examination. Future work will add peripheral blood cytogenetics/genetics, EUMDS-based prospective validation, and prognostication.

6. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19The ATTACC, ACTIV-4a, and REMAP-CAP Investigators (NEJM 08/2021)

ATTACC Investigators et al.

BACKGROUND

Thrombosis and inflammation may contribute to the risk of death and complications among patients with coronavirus disease 2019 (Covid-19). We hypothesized that therapeutic-dose anticoagulation may improve outcomes in noncritically ill patients who are hospitalized with Covid-19.

METHODS

In this open-label, adaptive, multiplatform, controlled trial, we randomly assigned patients who were hospitalized with Covid-19 and who were not critically ill (which was defined as an absence of critical care–level organ support at enrollment) to receive pragmatically defined regimens of either therapeutic-dose anticoagulation with heparin

or usual-care pharmacologic thromboprophylaxis. The primary outcome was organ support–free days, evaluated on an ordinal scale that combined in-hospital death (assigned a value of −1) and the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge. This outcome was evaluated with the use of a Bayesian statistical model for all patients and according to the baseline d-dimer level.

RESULTS

The trial was stopped when prespecified criteria for the superiority of therapeutic-dose anticoagulation were met. Among 2219 patients in the final analysis, the probability that therapeutic-dose anticoagulation increased organ support–free days as compared with usual-care thromboprophylaxis was 98.6% (adjusted odds ratio, 1.27; 95% credible interval, 1.03 to 1.58). The adjusted absolute between-group difference in survival until hospital discharge without organ support favoring therapeutic-dose anticoagulation was 4.0 percentage points (95% credible interval, 0.5 to 7.2). The final probability of the superiority of therapeutic-dose anticoagulation over usual-care thromboprophylaxis was 97.3% in the high d-dimer cohort, 92.9% in the low d-dimer cohort, and 97.3% in the unknown d-dimer cohort. Major bleeding occurred in 1.9% of the patients receiving therapeutic-dose anticoagulation and in 0.9% of those receiving thromboprophylaxis.

CONCLUSIONS

In noncritically ill patients with Covid-19, an initial strategy of therapeutic-doe anticoagulation with heparin increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support as compared with usual-care thromboprophylaxis.

---

7. Poziotinib for Patients With HER2 Exon 20 Mutant Non–Small-Cell Lung Cancer: Results From a Phase II Trial. JCO 09/2021

Yasir Y. Elamin, MD; Jacqulyne P. Robichaux, PhD; Brett W. Carter, MD; Mehmet Altan, MD; Don L. Gibbons, MD, PhD; Frank V. Fossella, MD; Vincent K. Lam, MD; Anisha B. Patel, MD; Marcelo V. Negrao, MD; Xiuning Le, MD, PhD; Frank E. Mott, MD; Jianjun Zhang, MD, PhD; Lei Feng, PhD; George Blumenschein Jr, MD; Anne S. Tsao, MD; and John V. Heymach, MD, PhD

PURPOSE

Targeted therapies against non–small-cell lung cancer (NSCLC) harboring *HER2* mutations remain an unmet need. In this study, we assessed the efficacy and safety of poziotinib in patients with *HER2* exon 20 mutant advanced NSCLC in a single-arm, open-label, phase II study.

PATIENTS AND METHODS

Patients with advanced *HER2* exon 20 mutant NSCLC were enrolled to receive poziotinib at a dose of 16 mg/d for 28-day cycles. The primary end point was objective response rate per RECIST version 1.1. Confirmatory scans were performed at least 28 days from initial radiologic response.

CONCLUSION

Poziotinib showed promising antitumor activity in patients with HER2 exon 20 mutant NSCLC including patients who had previously received platinum-based chemotherapy.

---

8. Radioembolization With Chemotherapy for Colorectal Liver Metastases: A Randomized, Open-Label, International, Multicenter, Phase III Trial. JCO 09/2021

Mary F. Mulcahy , MD1; Armeen Mahvash , MD2; Marc Pracht , MD3; Amir H. Montazeri, MD4; Steve Bandula , MD, PhD5; Robert C. G. Martin II, MD6; Ken Herrmann, MD7; Ewan Brown , MD8; Darryl Zuckerman, MD9; Gregory Wilson, MD10; Tae-You Kim, MD11; Andrew Weaver, MD12; Paul Ross, MD13; William P. Harris, MD14; Janet Graham, MD15; Jamie Mills, MD16; Alfonso Yubero Esteban, MD17; Matthew S. Johnson, MD18; Constantinos T. Sofocleous , MD19; Siddharth A. Padia, MD20; Robert J. Lewandowski, MD21; Etienne Garin , MD22; Philip Sinclair, PhD23; and Riad Salem , MD, MBA21; for the EPOCH Investigators

PURPOSE

To study the impact of transarterial Yttrium-90 radioembolization (TARE) in combination with second-line systemic chemotherapy for colorectal liver metastases (CLM).

METHODS

In this international, multicenter, open-label phase III trial, patients with CLM who progressed on oxaliplatin- or irinotecan-based first-line therapy were randomly assigned 1:1 to receive second-line chemotherapy with or without TARE. The two primary end points were progression-free survival (PFS) and hepatic PFS (hPFS), assessed by blinded independent central review. Random assignment was performed using a web- or voice-based system stratified by unilobar or bilobar disease, oxaliplatin- or irinotecan-based first-line chemotherapy, and KRAS mutation status.

RESULTS

Four hundred twenty-eight patients from 95 centers in North America, Europe, and Asia were randomly assigned to chemotherapy with or without TARE; this represents the intention-to-treat population and included 215 patients in the TARE plus chemotherapy group and 213 patients in the chemotherapy alone group. The hazard ratio (HR) for PFS was 0.69 (95% CI, 0.54 to 0.88; 1-sided P = .0013), with a median PFS of 8.0 (95% CI, 7.2 to 9.2) and 7.2 (95% CI, 5.7 to 7.6) months, respectively. The HR for hPFS was 0.59 (95% CI, 0.46 to 0.77; 1-sided P < .0001), with a median hPFS of 9.1 (95% CI, 7.8 to 9.7) and 7.2 (95% CI, 5.7 to 7.6) months, respectively. Objective response rates were 34.0% (95% CI, 28.0 to 40.5) and 21.1% (95% CI, 16.2 to 27.1; 1-sided P = .0019) for the TARE and chemotherapy groups, respectively. Median overall survival was 14.0 (95% CI, 11.8 to 15.5) and 14.4 months (95% CI, 12.8 to 16.4; 1-sided P = .7229) with a HR of 1.07 (95% CI, 0.86 to 1.32) for TARE and chemotherapy groups, respectively. Grade 3 adverse events were reported more frequently with TARE (68.4% v 49.3%). Both groups received full chemotherapy dose intensity.

CONCLUSION

The addition of TARE to systemic therapy for second-line CLM led to longer PFS and hPFS. Further subset analyses are needed to better define the ideal patient population that would benefit from TARE.

---

9. Management of the Axilla in Early-Stage Breast Cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline

Muriel Brackstone, MD, PhD; Fulvia G. Baldassarre, MSc; Francisco E. Perera, MD; Tulin Cil, MD, MEd; Mariana Chavez Mac Gregor, MD, MSc; Ian S. Dayes, MD; Jay Engel, MBBCh; Janet K. Horton, MD; Tari A. King, MD; Anat Kornecki, MD; Ralph George, MD; Sandip K. SenGupta, MD; Patricia A. Spears, BS; and Andrea F. Eisen, MD

PURPOSE

To provide recommendations on the best strategies for the management and on the best timing and treatment (surgical and radiotherapeutic) of the axilla for patients with early-stage breast cancer.

METHODS

Ontario Health (Cancer Care Ontario) and ASCO convened a Working Group and Expert Panel to develop evidence-based recommendations informed by a systematic review of the literature.

RESULTS

This guideline endorsed two recommendations of the ASCO 2017 guideline for the use of sentinel lymph node biopsy in patients with early-stage breast cancer and expanded on that guideline with recommendations for radiotherapy interventions, timing of staging after neoadjuvant chemotherapy (NAC), and mapping modalities. Overall, the ASCO 2017 guideline, seven high-quality systematic reviews, 54 unique studies, and 65 corollary trials formed the evidentiary basis of this guideline.

RECOMMENDATIONS

Recommendations are issued for each of the objectives of this guideline: (1) To determine which patients with early-stage breast cancer require axillary staging, (2) to determine whether any further axillary treatment is indicated for women with early-stage breast cancer who did not receive NAC and are sentinel lymph node–negative at diagnosis, (3) to determine which axillary strategy is indicated for women with early-stage breast cancer who did not receive NAC and are pathologically sentinel lymph node–positive at diagnosis (after a clinically node-negative presentation), (4) to determine what axillary treatment is indicated and what the best timing of axillary treatment for women with early-stage breast cancer is when NAC is used, and (5) to determine which are the best methods for identifying sentinel nodes.

THE BOTTOM LINE

10. Management of the Axilla in Early-Stage Breast Cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline

Muriel Brackstone, MD, PhD; Fulvia G. Baldassarre, MSc; Francisco E. Perera, MD; Tulin Cil, MD, MEd; Mariana Chavez Mac Gregor, MD, MSc; Ian S. Dayes, MD; Jay Engel, MBBCh; Janet K. Horton, MD; Tari A. King, MD; Anat Kornecki, MD; Ralph George, MD; Sandip K. SenGupta, MD; Patricia A. Spears, BS; and Andrea F. Eisen, MD

GUIDELINE OBJECTIVES

To provide recommendations on the best strategies for the management and on the best timing and treatment (surgical and radiotherapeutic) of the axilla in early-stage breast cancer. Specific objectives are presented before each recommendation.

TARGET POPULATION

Patients with early-stage breast cancer (ie, stages I, IIA, and IIB; prognostic groups T1, T2, N0, N1mi, N1, and M0; and primary tumor size ≤ 5 cm).

TARGET AUDIENCE

Surgeons, radiation oncologists, medical oncologists, and other clinicians (eg, pathologists, radiologists, oncology nurses, and genetic counselors) involved in the staging, radiation, and systemic treatment and in the management of the axilla in patients with early-stage breast cancer.

METHODS

A joint OH (CCO) and ASCO Expert Panel was convened to develop clinical practice guideline recommendations on the basis of a systematic review of the medical literature.

PREAMBLE TO RECOMMENDATIONS

The focus of this guideline is the management of the axilla in patients with early-stage breast cancer. This includes interventions such as surgery, radiotherapy, imaging, and systemic treatment. For all recommendations, we recommend a patient-centered approach. Each recommendation corresponds to a specific objective of this guideline. An algorithm for the management of the axilla in patients with early-stage breast cancer is presented in Figure 1.

RECOMMENDATIONS

Objective 1

To determine which patients with early-stage breast cancer require axillary staging.

Recommendation 1

- For patients age ≥ 70 years with clinically node-negative (T1N0) early-stage invasive breast cancer, that is hormone receptor–positive and human epidermal growth factor receptor 2 (HER2)–negative, SLNB is not required. This is supported by the Choosing Wisely statement released on July 12, 2016, and updated on June 20, 2019, by the Society of Surgical Oncology[8] that stated, "Don't routinely use sentinel node biopsy in clinically node negative women ≥ 70 years of age with early stage hormone receptor positive, HER2 negative invasive breast cancer" if they will be treated with hormonal therapy. If omission of SLNB is considered, a consultation with a medical oncologist can be considered before surgery to discuss hormonal therapy (Type: informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).
- For patients age < 70 years without significant competing comorbidities, SLNB should be considered for axillary staging of early-stage breast cancer (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate to high for staging by ALND v no ALND; insufficient for staging by SLNB v no staging; Strength of recommendation: strong).

Qualifying Statement for Recommendation 1

- The information acquired from SLNB would be helpful in guiding adjuvant treatment decision making.
- Patients should be evaluated on a case-by-case basis to ensure appropriate patient-centered decision making.
- Patients who are clinically node-negative on physical examination but are found to be sonographically abnormal on imaging with or without confirmatory biopsy can be offered SLNB as first-line axillary staging.

Objective 2

To determine whether any further axillary treatment is indicated for women with early-stage breast cancer who did not receive NAC and are sentinel lymph node–negative at diagnosis.

Recommendation 2

- Clinicians should not recommend ALND for women with early-stage breast cancer who do not have nodal metastases (endorsed from Recommendation 1 of the ASCO 2017 update guideline) (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).
- In some selected patients (eg, patients with medially or centrally located tumors or with high-risk features), and using a patient-centered approach, it is reasonable to offer the option of LRNI to include at least the supraclavicular and ipsilateral internal mammary lymph nodes in addition to the breast and/or chest wall (see the Qualifying Statement). For the majority of patients (ie, node-negative patients whose tumors are not medial or central in location and who do not have other high-risk features), we cannot recommend LRNI. A risk-benefit discussion should be undertaken on a case-by-case basis for these patients (see the Qualifying Statement) (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate to low; Strength of recommendation: weak).

Qualifying Statement for Recommendation 2

Surgical interventions

- SLNB is currently the standard of practice for this population.
- The evidence regarding the omission of ALND upon which this recommendation is based did not include patients who had a history of another cancer, had a multicentric breast cancer, had a prior ipsilateral breast cancer surgery or prior ipsilateral axillary surgery, were age < 18 or > 80 years, were pregnant or lactating, were allergic to blue dye or radioisotope, had evidence of metastatic disease, had tumors > 3 cm in diameter, suffered from chronic life-threatening diseases possibly preventing the use of adjuvant therapy, had stage T0 tumors (ie, ductal carcinoma in situ), had multifocal tumors, and received previous NAC. For these patients, decisions regarding ALND should be made after discussion between patient and clinicians on a case-by-case basis, depending on the invasive component of the lesion, other clinical circumstances, and patient preferences.

Radiotherapy interventions

- Patients with centrally or medially located tumors may modestly benefit (< 5% difference) from LRNI compared with whole-breast irradiation (WBI) only (postlumpectomy) or no postoperative radiation (postmastectomy) in terms of DFS, distant DFS, and locoregional relapse, but not in terms of overall survival (OS).
- Postmastectomy patients with node-negative, triple-negative breast cancer who receive chemotherapy may benefit from chest wall radiotherapy compared with no radiotherapy in DFS and OS.
- A radiotherapy dose fractionation schedule of 50 Gy in 25 fractions over 5 weeks is the current standard used in the relevant clinical trials; however, we recognize that there are other regimens now considered clinically appropriate and/or equivalent to this traditional fractionation.

Objective 3

To determine which axillary strategy is indicated for women with early-stage breast cancer who did not receive NAC and are pathologically sentinel lymph node–positive at diagnosis (after a clinically node-negative presentation).

Recommendation 3

(A) No further axillary surgery beyond SLNB compared with ALND

Clinicians should not recommend ALND for women with early-stage breast cancer who have one or two sentinel lymph node metastases and will receive breast-conserving surgery with conventionally fractionated whole-breast radiotherapy (endorsed from ASCO 2017 guideline,[9,10]

Recommendation 2.1) (Type: evidence based; benefits outweigh harms; Evidence quality: high for patients who received breast-conserving surgery; Strength of recommendation: strong for those who had breast-conserving surgery. For patients who had mastectomy and for those excluded from the trials, the strength of the body of the evidence is insufficient and the recommendation is weak).

(B) Radiotherapy of the axilla (LRNI) compared with no LRNI

It is reasonable to offer the option of treating the axilla with radiotherapy in addition to breast or chest wall irradiation following surgery, particularly in patients with medial or central tumors and in patients with high-risk features. Discussion of pros and cons with patients needs to occur, and the decision should be made on a case-by-case basis (Type: evidence based; benefits may outweigh harms; Evidence quality: low; Strength of recommendation: weak).

(C) Radiotherapy to the axilla compared with further surgery (ALND)

We recommend radiotherapy of the axilla in lieu of ALND in patients who are clinically node-negative and pathologically sentinel lymph node–positive with tumors of up to 5 cm and unifocal or multifocal disease restricted to one quadrant. In patients who receive breast-conserving surgery, we recommend no ALND if one or two sentinel lymph nodes are positive. LRNI is a reasonable option, especially when there are high-risk features as in (B). ALND and LRNI to the axilla are recommended if ≥ 3 sentinel lymph nodes are positive. In patients who receive mastectomy and have one to two positive nodes, postmastectomy radiation (PMRT) to the axilla is recommended and ALND can be safely omitted. In patients declining PMRT (ie, patients with immediate reconstruction), either radiation to the axilla without the chest wall or completion ALND can be considered. In patients who receive mastectomy and have ≥ 3 positive nodes, ALND followed by LRNI can be considered (Type: informal consensus; benefits outweigh harms in the short term; Evidence quality: low; Strength of recommendation: weak).

(D) Radiotherapy compared with no treatment

In patients with unilateral invasive cancer of small size (ie, T1a), favorable tumor features (eg, estrogen receptor–positive undergoing hormonal therapy), clear margins, and one to three positive nodes, treated with chemotherapy or hormonal therapy, clinicians might offer the option of omitting LRNI (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: weak).

Qualifying Statement for Recommendation 3

(A) No further axillary surgery beyond SLNB compared with ALND

- The evidence upon which this recommendation is based did not include patients who were pregnant or breastfeeding, had a history of another malignancy in the previous 5 years, have bilateral breast cancer, have multicentric disease, have three or more positive sentinel lymph nodes, have a concomitant malignancy, previously received systemic therapy for breast cancer, received chemoprevention in the preceding year, have distant metastases or macrometastatic disease, have palpable axillary nodes, and were < 18 or > 75 years old.

For these patients, as well as for patients who are treated with mastectomy, decisions regarding completion of ALND should be made after discussion between patient and clinicians on a case-by-case basis depending on the invasive component of the lesion, other clinical circumstances, and patient preferences, taking into account the limited data specific to mastectomy and considering that these recommendations represent an extrapolation, on the basis of expert opinion, from trials designed for patients undergoing breast-conserving surgery.

- The management of the axilla for patients with four or more positive lymph nodes (N2 and N3 disease) falls outside the scope of this guideline. Please refer to OH (CCO) Program in Evidence-Based Care (PEBC) guideline 19-1 guideline: locoregional therapy of locally advanced breast cancer (LABC).[11] For exactly three positive lymph nodes, there is not enough evidence to make a recommendation, and therefore, we recommend proceeding with ALND and considering LRNI.

(B) LRNI compared with no LRNI

Patients with estrogen receptor–negative (ER–) and progesterone receptor–negative (PR–) status may have a more favorable DFS when treated with LRNI in addition to surgery.

(C) Radiotherapy to the axilla compared with further surgery (ALND)

The ongoing MA39 (NCT00005957) study addresses the incremental benefit of LRNI of the axilla in lower-risk, node-positive patients. At this time, no studies comparing SLNB alone without LRNI have been identified in the mastectomy or lumpectomy setting.

(D) Radiotherapy compared with no treatment

- Patients age ≥ 65 years may benefit less from the addition of radiotherapy.
- Receptor–negative patients may benefit more from radiotherapy treatment.

Objective 4

To determine what axillary treatment is indicated and what the best timing of axillary treatment for women with early-stage breast cancer is when NAC is used.

Recommendation 4

(A) Initially node-negative patients

- Patients who are initially clinically node-negative on physical examination, and those who had clinically suspicious nodes on physical examination but deemed to be pathologically negative at fine needle aspiration or core needle biopsy, and were treated with NAC should receive SLNB at the time of surgery as their axillary staging procedure (Type: informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong).

(B) Initially node-positive patients

- For patients who were initially clinically and biopsy-proven node-positive, and who remained clinically node-positive after NAC, we recommend ALND.
- For patients who were initially clinically and biopsy-proven node-positive, and became node-negative after NAC, we recommend SLNB to restage the axilla. Restaging can be achieved by placing a biopsy clip into the biopsied positive node at diagnosis and localizing it at surgery along with sentinel node biopsy or, in institutions where the use of biopsy clips for nodes is not available, by performing sentinel node biopsy with dual tracer and excising at least three sentinel nodes to minimize the false-negative rate (FNR) and optimize accuracy of the procedure. At this time, we also recommend LRNI for these patients, regardless of pathologic status of sentinel lymph nodes.

- Postmastectomy patients who are node-positive on surgical pathology after NAC can be offered PMRT after a completion ALND.
- We recommend LRNI for the postmastectomy node-positive cohort after NAC while awaiting data from ongoing trials (ie, the MAC19 study).
- We recommend LRNI after ALND for patients clinically and biopsy-proven node-positive at breast-conserving surgery who remain pathologically node-positive after NAC.
- Shared decision-making processes should be put in place while we await mature clinical trial data, to enable patient value-based decision making.

(Type: evidence based; benefits outweigh harms; Evidence quality: low; Strength of recommendation: weak.)

(C) SLNB timing: before or after NAC

We recommend against performing lymph node sampling twice, before and after NAC. We recommend to time the SLNB after NAC and not before in clinically node-negative patients who will receive NAC (Type: informal consensus; benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

Qualifying statement for Recommendation 4

(B) Initially clinically positive and biopsy-proven node-positive patients

- To date, the clinical standard of care for node-positive patients who fail to respond clinically in the axilla to NAC requires maximal therapy to the axilla, which includes ALND followed by LRNI.

Objective 5

To determine which are the best methods for identifying sentinel nodes.

Recommendation 5

(A) Single versus dual tracer

For patients having primary surgery, we recommend using a sentinel node tracer (eg, it is not necessary to add blue dye on a regular basis for SLNB if the radiocolloid signal successfully identifies the sentinel node(s) in the axilla). In cases of nonidentification, blue dye can be added. Screening for radiocolloid signal before incision is recommended, and blue dye can be added before making the incision. In patients who receive NAC, we recommend either placing a biopsy clip into the positive node at diagnosis and localizing it at time of surgery or using dual tracer (radiocolloid plus blue dye) (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

(B) US-guided staging versus standard guided (dye or isotope) staging

In clinically node-negative patients with early-stage breast cancer where the sentinel lymph node is likely to be negative (ie, T1 and T2), preoperative axillary US staging is not recommended.

In patients with clinically palpable (ie, clinically positive) lymph nodes, it is recommended to conduct US-guided core biopsy of the axillary node to prove pathologic positivity. If patients are pathologically negative on image-guided lymph node biopsy, see Recommendation 2. If they are pathologically positive on image-guided lymph node biopsy, see Recommendation 3 (Type: evidence based; benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

(C) US-guided staging versus surgical staging

We recommend that diagnostic staging by US only (ie, not confirmed by a biopsy) should not be used instead of traditional SLNB staging (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Qualifying statement for Recommendation 5

(A) Dual tracer should be used in settings where it is expected to be a learning curve for the operators performing the procedure (eg, low-volume centers and surgeons in training or post-training).

(C) If a clip is used to identify a biopsied lymph node at diagnosis, the node containing the clip needs to be localized to make sure that it is excised. If dual tracer is used, three or more sentinel nodes have to be identified. If three or more sentinel nodes are not identified in a patient who has had NAC according to standard sentinel lymph node techniques, an axillary dissection is recommended.