U.S. Food and Drug Administration
Center for Devices and Radiological Health

General & Plastic Surgery Devices Meeting
Summary of the Meeting in Relation to the ProSense™ Cryoablation System
November 7, 2024

Introduction

On November 7, 2024, the FDA's General and Plastic Surgery Devices Panel met in person to discuss, make recommendations, and vote on clinical information related to a De Novo request for the ProSense™ Cryoablation System sponsored by IceCure Medical Limited, which is a cryosurgical tool for the treatment of tumors in interventional oncology. The Panel's discussion focused on the sponsor's proposed indication "for use in the treatment of patients with early stage, low-risk breast cancer for the treatment of breast cancer with adjuvant endocrine therapy."

Dr. Hobart Harris, Chair, introduced himself, noted for the record that members constituted a quorum, and proceeded with the introductions of the members identified in the meeting roster.

Ms. Candace Nalls, Designated Federal Officer for the Panel, read the Conflict of Interest Statement and stated that all members and consultants of the Committee are subject to federal conflict of interest laws and regulations, and that the FDA has determined that all of them are in compliance with such laws. No conflict-of-interest waivers have been issued.

External Speakers Presentations

Dr. Monica Morrow's Presentation

Dr. Morrow's presentation highlights the significant evolution of breast cancer treatment over the past 35 years, with a particular focus on locoregional therapy, including breast surgery and radiotherapy. She explains how breast surgery has shifted from the radical mastectomy to more conservative options, including total mastectomy, breast-conserving surgery, and reconstruction. This shift was influenced by Dr. Bernie Fisher's "systemic disease hypothesis" in the 1970s, which challenged the belief that local control alone determined survival, the Halstedian hypothesis of breast cancer biology. The NSABP B-04 trial played a pivotal role in validating the use of modified radical mastectomy and set the stage for breast-conserving surgery and adjuvant systemic therapies.

In terms of radiotherapy, Dr. Morrow notes its standardization after breast-conserving surgery, especially through the results of the NSABP B-06 trial, which demonstrated that lumpectomy combined with radiation offered survival rates comparable to mastectomy. While some trials, such as the Milan III and B21 trials, examined the possibility of omitting radiotherapy in low-risk patients, other studies (e.g., CALGB 9343

and Toronto-British Columbia) found that radiotherapy could be safely avoided in some older hormone receptor positive patients.

Dr. Morrow also emphasizes that breast cancer is not a single disease, but rather a collection of genetically distinct diseases. Treatment approaches, therefore, must be tailored to the tumor's biology, considering factors like ER/PR and HER2 status. Studies like LUMINA, IDEA, and DEBRA have explored the use of biological markers, such as Ki-67 and Oncotype scores, to assess whether radiotherapy can be safely omitted in low-risk, hormone receptor positive patients, further refining treatment strategies based on tumor biology.

When discussing axillary surgery, Dr. Morrow explains that the routine use of axillary dissection no longer improves survival. The TAILORx and RxPonder studies showed that chemotherapy may not benefit all patients, allowing for less invasive approaches like sentinel node biopsy. Additionally, the SOUND trial confirmed that axillary surgery can often be safely avoided in patients with clinically negative nodes, with no significant impact on outcomes.

Finally, Dr. Morrow touches on the development of partial-breast irradiation, which has become an important alternative to whole-breast irradiation. This approach reduces treatment duration and side effects while offering similar local recurrence rates and reduced toxicity, particularly for early-stage, ER+ cancers.

In conclusion, Dr. Morrow highlights how ongoing research, along with advances in screening, systemic therapies, and a deeper understanding of tumor biology, has facilitated the de-escalation of surgery and radiotherapy. These advancements have led to more personalized treatment options that balance intensity with the patient's health and quality of life, making tumor characteristics and patient preferences central to decision-making in breast cancer treatment.

Dr. Julie A. Margenthaler's Presentation

Dr. Margenthaler's presentation focused on the risk factors and mechanisms of locoregional recurrence in breast cancer, emphasizing the roles of patient characteristics, tumor biology, and molecular subtypes. She began by discussing the anatomical and histopathological factors influencing recurrence risk, noting that most breast cancers arise from ductal and lobular units. The distinction between in situ and invasive tumors was highlighted, with invasive tumors being graded based on characteristics such as nuclear pleomorphism and mitotic rate, which correlate with prognosis and recurrence risk.

She then reviewed key clinical trials comparing breast-conserving therapy with mastectomy, such as the B-06 trial, which demonstrated that radiation therapy significantly reduced locoregional recurrence in breast-conserving therapy patients, though over 10% still experienced recurrence. Other studies like the Milan III, NCI, and EORTC 10801 trials confirmed that factors such as tumor size, adjuvant radiation, and patient characteristics heavily influenced recurrence outcomes. Despite differences in recurrence rates, breast-conserving therapy combined with radiation was shown to provide survival outcomes equivalent to mastectomy.

Dr. Margenthaler highlighted the importance of patient-specific factors in predicting recurrence risk. Younger patients, larger tumors, and positive lymph nodes were associated with higher locoregional recurrence rates. Hormone receptor negative tumors and more aggressive disease also contributed to poorer prognoses and higher recurrence risks. Most recurrences occur within the first five years, although late recurrences beyond 10 years remain clinically significant.

The presentation also delved into molecular subtyping, referring to Charles Perou's 2000 study that classified breast cancer into five intrinsic subtypes: luminal A, luminal B, HER2-enriched, triple-negative, and normal-like. These subtypes exhibit distinct recurrence patterns, with HER2-enriched cancers tending to recur locoregionally earlier, while triple-negative cancers are associated with both locoregional and distant recurrences, particularly in the early years post-treatment. Even luminal A cancers, though generally favorable, can demonstrate late recurrences, reinforcing the need for long-term surveillance.

In conclusion, Dr. Margenthaler emphasized the importance of combining traditional pathological assessments with molecular subtyping to better understand and predict locoregional recurrence risks. Despite advances in systemic and radiation therapies reducing recurrence rates, locoregional recurrence remains an important factor influencing both survival and treatment decisions.

Dr. Patricia A. Ganz's Presentation

Dr. Ganz discussed the impact of breast cancer treatment and recurrence on patient outcomes, emphasizing quality of life. She began by outlining historical trends, noting the increased attention on quality of life as treatments became more intensive, involving surgery, radiation, chemotherapy, and endocrine therapy. A conceptual model from the 1990s highlighted four quality of life domains: physical functioning, psychological functioning, treatment side effects, and social functioning. Dr. Ganz explained that patients' assessments of their global quality of life often depend on their personal evaluation of these domains, which underscores the importance of asking targeted questions beyond general quality of life inquiries.

Dr. Ganz presented findings from a randomized trial focused on women completing breast cancer treatment. These women expressed concerns about treatment effectiveness, energy recovery, follow-up plans, and feeling misunderstood by family members. The study revealed significant differences in quality-of-life outcomes based on treatment types. Women undergoing mastectomy reported poorer physical functioning and higher pain levels than those who had lumpectomy, though mental health outcomes were similar across groups. Persistent symptoms, such as fatigue, joint pain, and body image dissatisfaction, were prevalent post-treatment and negatively influenced physical and mental health scores.

Over the past 20 years, advancements in treatment have led to less invasive approaches, particularly for early stage, low-risk breast cancer. More than half of cases now involve Stage 0 or 1 tumors, often requiring minimal treatment. However, extended treatment durations, such as adjuvant endocrine therapy lasting 5 to 10 years, can still lead to lingering symptoms like fatigue, neuropathy, cognitive issues, and anxiety in about 25%

of patients. Despite these challenges, quality of life generally returns to normal within a year after treatment for most patients.

Dr. Ganz also discussed trials evaluating the de-escalation of treatments, such as the DEBRA trial, which aims to determine whether omitting radiation in low-risk cases is non-inferior to standard therapy. Initial findings from the DEBRA trial suggest that most patients report good physical health and high quality of life post-lumpectomy, though some experience mild differences in breast texture and tenderness.

The presentation concluded with an exploration of the impact of cancer recurrence on quality of life. While recurrence leads to diminished physical and social functioning, patients often demonstrate psychological resilience. Data from Dr. Ganz's own research indicated declines in physical health and health perceptions after recurrence, but little change in emotional functioning. Women with metastatic recurrence faced greater challenges, yet many coped well due to familiarity with the healthcare system and prior cancer experience. Dr. Ganz highlighted that breast cancer today is often detected early through mammographic screening, with lumpectomy followed by shorter-duration radiation therapy as the standard treatment, and post-surgery symptoms are minimal and typically have little effect on quality of life. However, recurrence of breast cancer can lead to declines in physical and social functioning, poorer health perceptions, and symptoms like pain, fatigue, and insomnia, especially in metastatic cases. Despite this, most patients show psychological resilience.

Clarifying Questions

After the presentations, some members of the Panel asked clarifying questions. The experts' discussion during this section covered key aspects of breast cancer diagnosis and treatment. Topics that were touched include, among others, the reliability of core biopsies for genomic testing, challenges in detecting tumors due to pathology limitations, and the impact of surgical and radiation techniques on cosmetic outcomes and quality of life. The role of standardized surgical margins in reducing reoperations and improving cosmesis was also highlighted, as well as the relationship between local recurrence, survival outcomes, and modern systemic therapies.

IceCure Medical Ltd. Presentation

Introduction to IceCure Medical and the ProSense™ Cryoablation System

IceCure Medical specializes in minimally invasive cryoablation technologies. Their flagship product, ProSense™, is designed for tumor ablation, using liquid nitrogen to freeze and destroy cancerous tissues. It offers an alternative to traditional surgical options like lumpectomy, providing patients with a treatment associated with minimal pain, rapid recovery, and improved cosmetic results.

In the United States, the ProSense™ System has received FDA clearance for various tumor ablation procedures, including the treatment of breast fibroadenomas. It has

also gained approvals in numerous countries, including the European Union, Canada, and China. In 2021, ProSense™ received the FDA's Breakthrough Device Designation, acknowledging it as a promising treatment for early-stage breast cancer with potential advantages over conventional care.

Overview of the ICE3 Clinical Trial

The ICE3 trial, launched in 2014, is the largest prospective, multicenter, single-arm study focused on cryoablation for breast cancer. This study evaluated ProSense™'s safety and efficacy in treating early-stage, low-risk breast cancer in women aged 60 and above. The trial assessed cryoablation as a primary treatment without surgical excision.

Dr. Richard Fine, a key contributor to the ICE3 study design, noted that the study included 194 patients who met specific inclusion criteria, such as early-stage tumors ≤1.5 cm, estrogen and progesterone receptor-positive status, and HER2- status. Trial participants were monitored through follow-up assessments at six months, then annually for five years, with mammography and clinical evaluations as standard follow-up care.

Cryoablation Procedure and Patient Selection

Dr. Natalie Johnson, a prominent specialist in surgery for breast cancer and advocate for cryoablation, discussed the criteria for patient selection, emphasizing that ProSense™ is suitable for low-risk patients with favorable tumor biology. The ideal candidates are those with smaller tumors that are estrogen and progesterone receptor-positive and HER2-. This type of breast cancer typically responds well to endocrine therapy, allowing for de-escalated treatments.

Dr. Johnson reviewed the evolution of breast cancer treatments, noting the shift from extensive mastectomies to more conservative approaches, such as lumpectomy, which preserves the breast. Cryoablation is an extension of this trend, offering a less invasive option that involves only a small probe insertion, minimal cosmetic impact, and less disruption to patients' daily lives.

Technical Aspects of Cryoablation

Dr. Robert Ward, a diagnostic imaging expert, described the cryoablation procedure using the ProSense™ System, which involves inserting a probe into the tumor under real-time ultrasound guidance. The probe creates an ice ball around the tumor, achieving temperatures as low as -170 °C, which destroys the tumor. Throughout the procedure, measurements are taken to ensure the ice margin covers the entire tumor.

Imaging follow-ups, including ultrasound and MRI, show that the ablation zone gradually decreases over time as the body reabsorbs the treated tissue. Dr. Ward also presented earlier studies that demonstrated the safety and efficacy of cryoablation for tumors under 1.7 cm, which provided the foundation for the ICE3 trial.

Outcomes and Findings of the ICE3 Study

The ICE3 study reported high levels of effectiveness and safety. At the five-year mark, over 95% of patients were recurrence-free. Patients returned to normal activities quickly, with most resuming their routine within a day of the procedure. Both patients and physicians reported high satisfaction with cosmetic results, a significant advantage over traditional surgical methods.

Regarding adverse events, cryoablation exhibited a comparable safety profile to percutaneous breast biopsies. Common side effects were mild and included bruising, pain, and localized edema, with occasional occurrences of frost injury. Frost injury, which occurred in about 2% of patients, was easily managed by injecting saline to move the skin away from the ice ball during the procedure.

Comparative Analysis of Cryoablation and Lumpectomy

Dr. Fine compared ICE3 study outcomes to those reported for lumpectomy, showing that cryoablation offers a comparable recurrence rate but with faster recovery, lower pain, and better cosmetic outcomes. The study outcomes support cryoablation as a viable alternative for select patients, particularly those at low risk for breast cancer recurrence.

For women over 60 with low-risk, hormone-receptor-positive breast cancer, cryoablation could provide a patient-centered option, reducing the need for invasive surgery without compromising the efficacy of cancer treatment. Dr. Ward shared that cryoablation's advantages over lumpectomy include a reduced impact on physical appearance, faster recovery, fewer logistical challenges, and the option for patients to drive themselves to and from the procedure.

Regulatory Review and Expanded Indications

Expert in medical device regulatory affairs, Ms. Margeaux Rogers discussed the FDA's involvement, including post-hoc analyses and comparisons of ICE3 data with other studies. IceCure Medical submitted additional literature reviews and a meta-analysis showing that recurrence rates for cryoablation were similar to or slightly lower than those for lumpectomy without radiation.

The FDA's own systematic review emphasized lumpectomy outcomes and identified areas where cryoablation's performance differed slightly. Despite this, IceCure maintained that ICE3 results demonstrated the safety, efficacy, and comparable recurrence rates of cryoablation, reinforcing its value as a minimally invasive alternative for select patients.

Patient Perspective and Quality of Life Considerations

Dr. Johnson highlighted the patient-centered nature of cryoablation, noting that patients can return to daily activities immediately after the procedure. Cryoablation's cost, which is lower than lumpectomy, makes it more accessible for patients who need a quick, minimally invasive option.

Dr. Fine emphasized the importance of shared decision-making, allowing patients to weigh the benefits and risks of cryoablation against traditional surgery. The high levels of patient satisfaction and the cosmetic outcomes further support cryoablation as a compelling option for older patients who prioritize a minimally invasive treatment.

FDA Review and Benefit-Risk Considerations

The FDA's presentation highlighted key aspects of the ICE3 study and its implications for patient care. The agency acknowledged the potential quality-of-life benefits of cryoablation, particularly in reducing surgical invasiveness and improving recovery times. However, they raised concerns about the recurrence rates reported in the ICE3 trial compared to lumpectomy outcomes.

The FDA conducted a systematic review and meta-analysis, which compared lumpectomy and cryoablation outcomes, and revealed discrepancies and slight differences in recurrence rates across various patient subpopulations, raising questions about patient selection, methodology, and long-term efficacy.

Additionally, the FDA emphasized the need for robust data on specific subgroups, such as those receiving adjuvant endocrine therapy, to ensure ProSense™ provides a favorable benefit-risk balance. They invited the Panel to assess the device's overall safety and efficacy, while weighing the quality-of-life benefits of surgery avoidance against the risks of recurrence for the proposed patient population.

Future Implications and Accessibility

If FDA-approved, the ProSense™ System could become a widely available, minimally invasive treatment option for early-stage, low-risk breast cancer. Broader access through insurance coverage would reduce out-of-pocket costs for patients, making cryoablation more accessible to those in need.

Furthermore, approval would facilitate standardized training and educational programs, ensuring practitioners are equipped to implement the procedure safely and effectively. Cryoablation aligns with current trends in treatment de-escalation, offering patients a quality-of-life-focused alternative to traditional surgery.

Questions for FDA

Several key points were addressed during this session. The question of why the device was considered Class II under the De Novo process instead of Class III was raised. Dr. Carr explained that the De Novo classification takes into account whether special controls sufficiently mitigate risks, and the device's long clinical history supported its Class

II status. Clinical data is generally not required for Class II devices, though it could be necessary as a special control, and post-market surveillance, though uncommon, could be mandated if there are uncertainties in the benefit-risk analysis.

The discussion also touched on the role of IRBs in determining risk, with the FDA noting that IRBs can consult with the agency if needed but in this case, the IRB opted not to require an Investigational Device Exemption (IDE). Regarding cryoablation's prevalence beyond breast cancer, the FDA acknowledged the lack of real-world evidence on this broader use, though international studies had been reviewed.

A question about the exclusion of small studies from the systematic review was clarified by the FDA, which explained that study design, rather than participant size, was the basis for inclusion. The potential influence of small studies in the FDA's meta-analysis was also discussed, with the agency presenting a range of results from these studies rather than a single meta-estimate to avoid misleading conclusions.

Further questions addressed issues like the granularity of the device label and its linkage to endocrine therapy, with the FDA emphasizing the importance of defining low risk for recurrence. The recurrence rates in radiation-treated cohorts were also discussed, with the FDA noting that the small size of these cohorts complicated direct comparisons. The final clarification was provided regarding recurrence cases; no patients treated with radiation experienced recurrence, and two cases initially counted as recurrences did not actually involve radiation, as clarified by the FDA.

Open Public Hearing

Five public attendees were given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda:

1. **Dr. Zuckerman:** Representing the National Center for Health Research, Dr. Zuckerman expressed concern about the lack of randomized trials for the cryoablation system, citing data irregularities and insufficient diversity in study populations. She highlighted the importance of validated measures for quality of life and urged the FDA to ensure clear labeling and comprehensive informed consent tools for patients.

2. **Ms. Finnick:** As a breast cancer survivor, Ms. Finnick advocated for cryoablation as a less invasive treatment, sharing her positive personal experience with the procedure. She highlighted its minimal recovery time, lack of cosmetic impact, and the significant quality-of-life benefits compared to traditional surgical options.

3. **Ms. Shehar:** Describing her surgical experience for invasive ductal carcinoma, Ms. Shehar detailed the physical and emotional toll of her mastectomy and reconstruction, including scarring and ongoing challenges. She urged the FDA to make non-surgical options like cryoablation widely available to give patients more treatment choices.

4. **Ms. Smith:** An 88-year-old breast cancer survivor, Ms. Smith endorsed cryoablation based on her successful experience as part of a trial. She praised its non-invasive nature, minimal recovery time, and absence of disfigurement, advocating for FDA approval to increase access to this effective treatment.

5. **Dr. Tomkovich:** A radiologist with extensive experience in breast cryoablation and a co-principal investigator in the ICE3 trial, Dr. Tomkovich emphasized the safety, efficacy, and patient-centric nature of the procedure. He highlighted its growing acceptance in prestigious institutions and its potential to provide personalized, less invasive care while praising the bravery of patients who participated in the trial.

During the Panel discussion, Dr. Zuckerman emphasized the importance of patient education materials, advocating for clear, simple checklists to enhance informed consent, and expressed concerns about the moderate-risk classification of breast cancer treatments, arguing for randomized controlled trials (RCTs) to ensure rigorous evaluation. Dr. Alam supported the need for RCTs for comparability between treatments. In response, Dr. Tomkovich clarified that while the ICE3 trial was not randomized, its purpose was to validate cryoablation as comparable to the established gold standard of surgical lumpectomy, highlighting its direct comparison to well-established outcomes.

Panel Deliberations

The Panel discussed the design and outcomes of the ICE3 study, emphasizing the importance of a five-year clinical study with clear labeling for physicians and patients. While the study used a non-randomized, historical control trial design, panelists noted its limitations in a low-recurrence population. If redesigned, consulting the FDA for guidance would have been a priority. Long-term data beyond five years was limited, as were subgroup analyses, which showed no significant recurrence rate differences. However, the small sample size for racial groups limited broader conclusions.

Technical and procedural issues were also examined. Biopsy standards varied, typically requiring three or more cores based on the diagnostic physician's discretion. Post-cryoablation findings showed significant shrinkage of the ablation zone over time with no noticeable breast volume loss. Imaging modalities, particularly mammography, were deemed reliable for recurrence detection, with other methods used as needed. Concerns were raised about protocol violations and treatment exclusions, which were explained as instances of egregiously short treatment times or equipment malfunctions. One documented malfunction led to a single freeze procedure in 2019, with no recurrence observed in follow-up.

The Panel highlighted challenges in studying older populations, citing life expectancy and comorbidities as factors affecting long-term recurrence analysis. There was debate over whether cryoablation functions as a debulking procedure, with panelists ultimately categorizing it closer to a lumpectomy. Radiation therapy was noted as a standard of care for certain age groups, which some panelists felt should have been explicitly included in the indications for use. Meta-analyses comparing ICE3 with other

studies (e.g., LUMINA, Kunkler) revealed differences in recurrence rates, often influenced by whether radiotherapy was included in the patient regimen.

The Panel discussed the need for strong evidentiary standards in cancer treatment devices. Some members suggested incorporating long-term follow-up as a requirement for device approvals, while others questioned its utility for older populations. There was support for requiring patient education materials and checklists in device approval processes. Post-market surveillance was considered a critical tool for ensuring safety and effectiveness, though some felt pre-market evidence remains the gold standard. The process for rescinding device approvals was also clarified, with failures to meet post-marketing benchmarks identified as a potential cause for FDA compliance actions.

To conclude, while the ICE3 study demonstrated compliance and outcomes consistent with its design, the Panel emphasized the need for rigorous pre-market evidence, clear procedural guidelines, and long-term data collection to address gaps in evidence for low-recurrence populations.

Discussion on the FDA Questions.

Question 1: *Strengths and limitations of standard of care imaging technology to accurately characterize the tumor size prior to surgical or cryoablation treatment.*

Mammography and ultrasound were noted to typically underestimate tumor size by 2-3 mm, while MRI can show both over- and underestimations, with discrepancies ranging from 2-4 mm. The Panel highlighted the importance of accurate imaging for patient selection, though there was caution about over-relying on imaging due to its inherent limitations. For non-standard treatments like cryoablation or active monitoring of DCIS, imaging workups might be more comprehensive, potentially involving MRI or contrast-enhanced mammography, which could offer more precise measurements of tumor size and disease extent.

Despite acknowledging the general reliability of imaging, the Panel raised concerns about its precision and whether the standards or expectations for imaging should differ depending on the treatment approach. Additionally, there was a discussion on the regulatory aspects of De Novo devices, with considerations about benefit-risk data and the possibility of limited initial claims that could be expanded with post-marketing data.

Question 2: *Strengths and limitations of the single-arm, non-randomized study, performance goal and the reproducibility of the patient population.*

The Panel mentioned that, initially, a 5% local recurrence rate was considered reasonable, compared to the typical 8-10% recurrence rates in breast conservation. Although randomized trials are ideal, the Panel acknowledged that single-arm designs are often necessary in surgical trials due to challenges in randomizing patients. There was an emphasis on the difficulty of randomizing patients when the experimental treatment is already available outside of the trial, which could affect patient recruitment.

Concerns were raised about the trial's analysis, small event numbers, and the lack of a randomized control arm, particularly when substantial existing data on the control side could make a control arm less impactful. The need for reliable external data to assess the experimental treatment in comparison to standard treatments was highlighted. Some Panel members questioned whether patients might accept a slightly higher risk of recurrence to avoid radiation or endocrine therapy.

There were discussions about the importance of better defining the patient population using tools like Ki67, genomic tests, histopathological assessments, and imaging. However, concerns were raised about the trial's sample size and execution, especially regarding inclusion and exclusion criteria. Additionally, there were concerns about the lack of a randomized comparison between cryoablation and lumpectomy, questioning the potential benefits of the procedure given the small number of events in the trial. Variability in standard-of-care recurrence rates also made it difficult to establish a benchmark or determine acceptable risk.

Question 3: *Strengths and limitations of each analysis population and subpopulation for determining the benefit versus risk, alignment with the proposed indications for use and relative heterogeneity of subjects.*

It was noted that tools like Ki67 and genomic testing improve risk stratification, but concerns remain about standardizing follow-up and imaging protocols. Single-arm trials have limited sample sizes, and randomized trials would require impractically large populations. The heterogeneity of risk factors in the study was acknowledged, reflecting real-world patient diversity, which could influence the procedure's potential use if approved.

Some Panel members pointed out that de-escalation strategies, such as partial breast radiation, reflect a tolerance for some recurrence risk, and the observed recurrence rates in the study fall within the acceptable range typically communicated to patients. However, concerns were raised about the applicability of the procedure, particularly for older women, and potential inaccuracies in imaging, especially when measuring small differences in tumor size.

Concerns about bias and uncertainty in trials due to censoring were highlighted, as missing data can affect the robustness and accuracy of models. The absence of data on treatment parameter adherence, such as ice ball size and ablation time, was noted as a limitation, as it undermines the assessment of technical success and its impact on recurrence risk and generalizability. Additionally, concerns about selective patient inclusion, small sample sizes, age discrepancies, and the study's overall representativeness were raised, questioning the generalizability of the findings.

Question 4: *Clinical significance of the effectiveness results of the ICE3 study compared to the systematic literature.*

It was noted that while both the sponsor's and FDA's approaches to estimating outcomes have strengths and weaknesses, the FDA's reported 2.3% in-breast tumor recurrence rate aligns with literature estimates, with some caveats related to endocrine

therapy. However, concerns were raised about the lack of randomization in the study, reliance on aggregate data, and unaccounted prognostic factors, which could affect the interpretation of the results.

The importance of endocrine therapy compliance was highlighted, particularly when radiation is omitted. Clear definitions of how adherence to endocrine therapy impacts outcomes were deemed crucial, especially for patients opting for cryoablation over radiation or surgery. Panel members emphasized the need for guideline adherence, noting that younger patients with aggressive tumors may not be suitable candidates for such approaches.

The potential for patients to still receive radiation if necessary was clarified, but the importance of informed decision-making was emphasized. Patients should be made aware of factors influencing local recurrence rates, as some may accept a higher risk of recurrence in exchange for avoiding radiation or endocrine therapy. To improve patient understanding and ensure realistic treatment expectations, the Panel suggested the use of a registry to track outcomes and a specialized informed consent form.

Question 5: *How the adverse event data and cosmetic satisfaction surveys in the ICE3 study inform benefit and risk.*

Panel members noted that many patients are drawn to the treatment for its cosmetic benefits. However, there were concerns about the need for better guidance to facilitate informed decision-making. It was suggested that a clear patient information guide be included as part of special controls to ensure patients make well-informed choices, especially given that today's patients are more informed.

While the procedure was generally considered safe, there were calls for improved methodology and more formal measures of cosmesis to better assess cosmetic outcomes. It was pointed out that lumpectomy often provides excellent cosmetic results, suggesting that comparisons could be made in this area.

The safety of the procedure was affirmed, with references to its use in multiple countries and positive patient feedback regarding its acceptability. One of the members of the Panel emphasized the procedure's limited adverse effects, while also noting that surgery often has more significant long-term side effects that patients report post-treatment.

Question 6: *The quality-of-life benefits of surgery avoidance relative to the quality of life, risk of breast cancer recurrence.*

The discussion highlighted several key perspectives. Many patients, particularly in rural areas, expressed a preference for avoiding surgery, appreciating the quality-of-life benefits, such as less downtime and a less invasive treatment option. It was generally agreed that surgery avoidance could improve quality of life, especially for elderly patients or those with other health concerns.

However, the Panel emphasized that making informed decisions is crucial. Providing patients with sufficient information about their treatment options was highlighted as key to ensuring they understand both the benefits and risks. There was consensus that treatments like cryoablation are viable alternatives, but the risks, particularly regarding recurrence, need to be clearly communicated.

Some concerns were raised about the complexity of care when surgery is avoided. Increased imaging and biopsies could become necessary, adding layers of complexity to patient management. While cryoablation was considered comparable to other treatments, the lack of clear recurrence data in the trials made it more difficult to fully assess its long-term outcomes.

The Panel also agreed that patients should have the freedom to choose their treatment. Even if a local recurrence happens after opting for surgery avoidance, treatments like re-excision, radiotherapy, and other standard therapies remain available, offering options for salvage treatments.

Lastly, the Panel pointed out that current guidelines accept a 10% recurrence rate, as observed in studies like 9343 and PRIME 2, despite recommending no radiation. This adds further complexity, as the uncertainty around recurrence in the absence of radiation requires careful consideration when making treatment decisions.

Question 7: *Overall benefit-risk profile of the device for the proposed indications for use in the treatment of early-stage low-risk breast cancer in lieu of lumpectomy.*

The Panel discussed the overall benefit-risk profile of the device for treating early-stage low-risk breast cancer in place of lumpectomy, focusing on several key aspects. There was consensus on the need for clearer definitions of low-risk breast cancer, potentially incorporating genomic data to refine the benefit-risk assessment. While the real-world adoption of the technology suggests a favorable risk-benefit ratio, concerns were raised about the representativeness of biopsy specimens and the need for biopsy standardization, with suggestions for additional biopsies during cryoablation to improve tissue preservation.

There were also concerns regarding the appropriateness of the age limit for the device's use, with some members questioning whether the data supports the age range of 60-65 and suggesting further studies for younger or higher-risk populations. Although the device was supported for low-risk cases, doubts were raised about the sufficiency of evidence for approval, particularly regarding its use by non-specialists. Finally, there was an emphasis on the need for randomized controlled trials to better assess the treatment's effectiveness, particularly in terms of mortality, recurrence, and quality of life.

Panel Voting Session

Summary of the votes:

- 9 yes
- 5 no
- 0 abstain

Summary of the votes

The Panel's votes were divided, and some members expressed concerns about the uncertainty of recurrence risks and safety, particularly for patients in the 60-61 age range with longer life expectancy. Some recommended imposing age-based restrictions and conducting post-market studies to further evaluate long-term outcomes. Others were in favor, citing the procedure's potential for well-stratified, low-risk patients, though some raised concerns about the need for more targeted indications and stronger evidentiary standards.

Those who voted in favor acknowledged the procedure's benefits but also recognized the importance of gathering more detailed data. The varying perspectives reflected a shared desire for more comprehensive evidence to ensure the procedure's safety and effectiveness.

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I approve the minutes of the meeting as recorded in this summary.

Hobart W. Harris, M.D., M.P.H.
Voting Chair

I certify that I attended this meeting on November 7, 2024
and that these minutes accurately
reflect what transpired.

Candace J. Nalls -S

Digitally signed by Candace J. Nalls -S
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Candace Nalls, M.P.H.