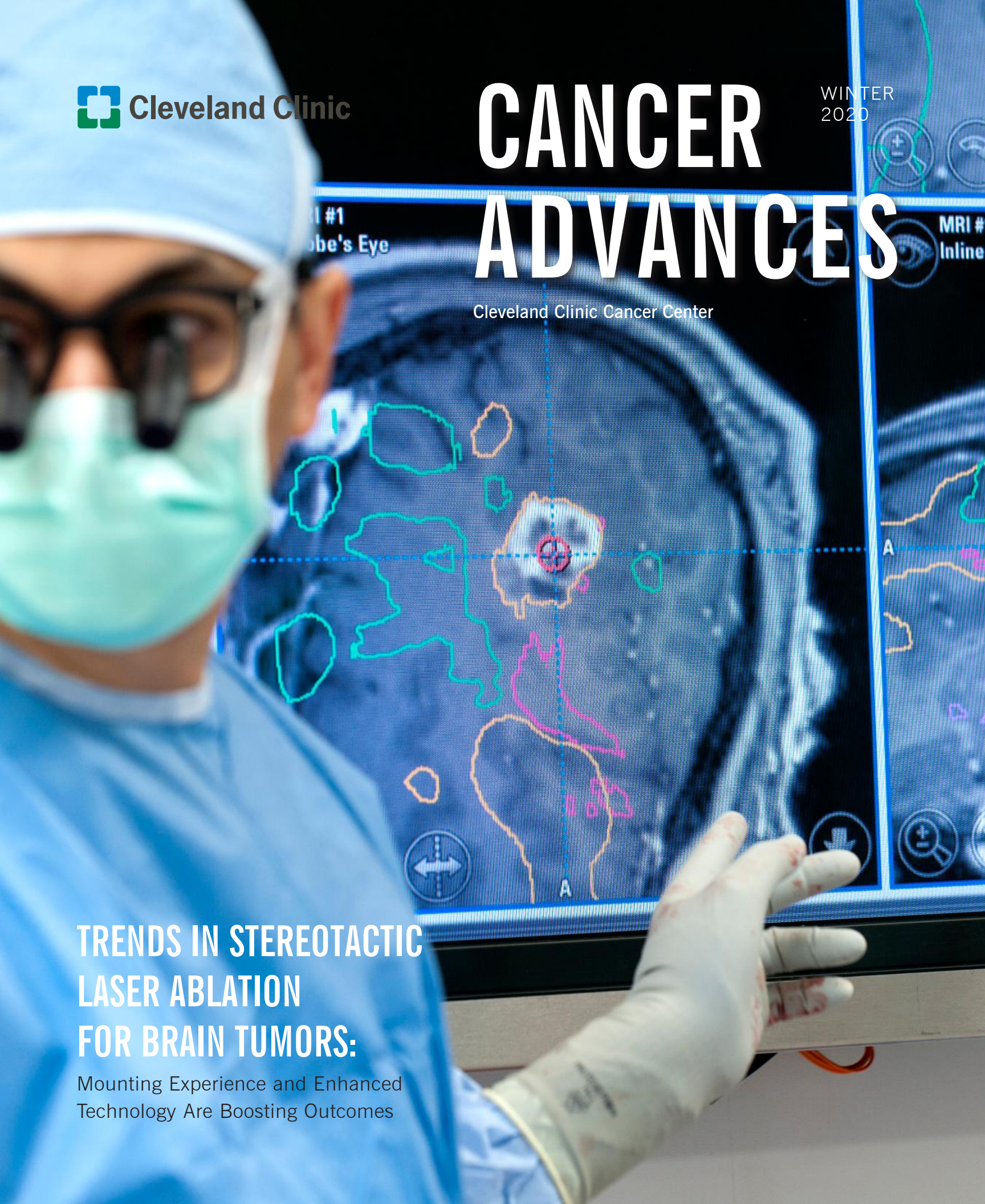
Cleveland Clinic

CANCER ADVANCES

WINTER
2020

Cleveland Clinic Cancer Center

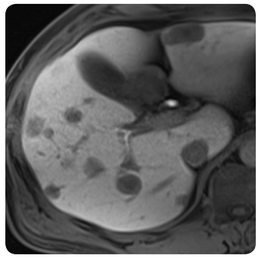


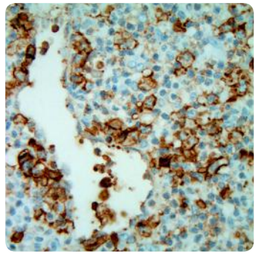
TRENDS IN STEREOTACTIC LASER ABLATION FOR BRAIN TUMORS:

Mounting Experience and Enhanced Technology Are Boosting Outcomes

Cleveland Clinic Cancer Center provides complete cancer care enhanced by innovative basic, genetic and translational research. It offers the most effective techniques to achieve long-term survival and improve patients' quality of life. The Cancer Center's more than 700 physicians, researchers, nurses and technicians care for thousands of patients each year and provide access to a wide range of clinical trials. Cleveland Clinic Cancer Center unites clinicians and researchers based in Taussig Cancer Institute and in Cleveland Clinic's 26 other clinical and special-expertise institutes, as well as cancer specialists at our regional hospitals, health centers and Cleveland Clinic Florida. Cleveland Clinic is a nonprofit academic medical center ranked as a top hospital in the country *(U.S. News & World Report)*, where more than 3,900 staff physicians and researchers in 180 specialties collaborate to give every patient the best outcome and experience.

INSIDE





ON THE COVER: Neurosurgeon Alireza Mohammadi, MD, of Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center.

DEAR COLLEAGUES,

BRIAN J. BOLWELL, MD, FACP
Chairman, Taussig Cancer Institute
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Improving cancer treatment for our patients depends on innovation and evaluation. We must be bold enough to attempt difficult things, and disciplined enough to honestly assess those efforts and respond accordingly. Informed risk-taking and rigorous appraisal go hand in hand. Both are essential if we are to continue making progress against this relentless disease.

The accounts in *Cancer Advances* reflect Cleveland Clinic Cancer Center's commitment to innovation and evaluation.

We were one of the early adopters of stereotactic laser ablation to treat brain tumors. The insights gained from nearly a decade's experience with this leading-edge and still-evolving tool are the subject of our cover story. Neurosurgeon Alireza M. Mohammadi, MD, reports (p. 24) that our outcomes and operative times have improved dramatically, even as our case mix has become more challenging.

We also are among the initial practitioners of a novel two-stage surgical strategy to treat liver cancer patients who do not qualify for traditional resection due to multicentric disease and an inadequate future liver remnant. Federico Aucejo, MD, Director of the Liver Cancer Program, describes (p. 16) this intriguing method.

Jame Abraham, MD, the newly appointed Chair of our Department of Hematology and Medical Oncology, is part of a multicenter team that has discovered (p. 4) a radiogenomic MRI signature that could identify HER2-positive breast cancer patients likely to benefit from targeted therapy.

Research (p. 8) conducted by Carol Burke, MD, Vice Chair of the Department of Gastroenterology, Hepatology and Nutrition, suggests the traditional formula for staging duodenal polyposis to predict cancer risk in familial adenomatous polyposis patients may need adjustment to account for previously unappreciated factors.

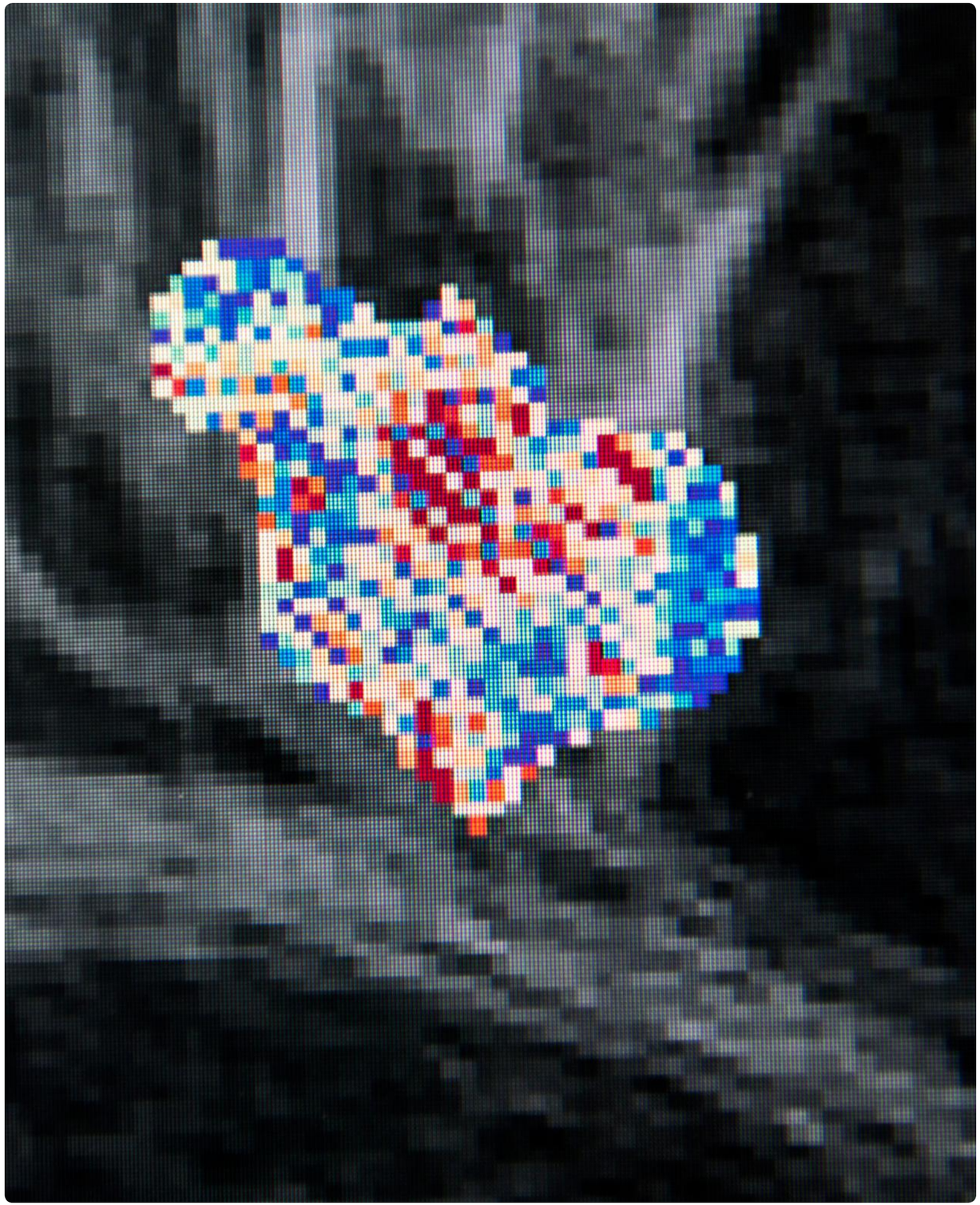
Importantly, these and other results detailed in *Cancer Advances* are impacting or will soon impact patient care. That tradition of translational research will be carried on in our new Center for Research Excellence in Gynecologic Cancer (p. 10), which will investigate a wide range of subjects, from targeted immunotherapy to the role of cancer stem cells.

None of this progress would be possible without the guidance of our many talented physician leaders. In my Chairman's Q&A (p. 28), I discuss our approach to physician leadership.

As always, I welcome opportunities to discuss the work we do and the possibility for collaboration. Please let us know how we can help.

Sincerely,

Brian J. Bolwell, MD, FACP | Chairman, Taussig Cancer Institute, Cleveland Clinic Cancer Center



NEW APPROACH MAY HELP PREDICT HER2+ TUMOR RESPONSE TO TREATMENT

Radiogenomic signature could identify patients likely to benefit from targeted therapy

KEY POINTS

HER2-targeted therapy has improved survival in human epidermal growth factor receptor 2-positive (HER2+) breast cancer, but some patients do not completely respond, and there is no clinically validated biomarker that predicts who is likely to benefit.

A multicenter team including Cleveland Clinic researchers has found that a radiogenomic signature on clinical dynamic contrast-enhanced magnetic resonance imaging can discriminate the response-associated HER2-enriched molecular subtype from other subtypes among patients with HER2+ tumors.

Subsequent evaluation of the imaging signature in recipients of HER2-targeted therapy found that it was associated with response to neoadjuvant chemotherapy.

If verified with additional research, the imaging signature could alter the course of treatment, with patients who are identified with nonresponsive HER2 molecular subtypes sent for surgical resection first and other treatments later.

A newly identified radiogenomic signature from human epidermal growth factor receptor 2-positive (HER2+) breast cancer tumors and their surrounding environment could serve as a future noninvasive method for predicting response to targeted treatment.

The emergence of HER2-targeted therapy, including the monoclonal antibodies trastuzumab and pertuzumab, has greatly improved survival in HER2+ breast cancer. Yet a significant percentage of patients will not achieve a complete preoperative response to a combination of anti-HER2 therapy and chemotherapy, and no clinically validated biomarker is currently available to indicate which patients are likely to benefit from targeted therapies.

Breast radiogenomics — an investigational diagnostic approach that integrates genomic data and qualitative analysis of clinical radiology for tumor characterization — has shown promise in noninvasively identifying patients' genetic profile from imaging, but has not been applied in the context of predicting clinical outcomes and guiding targeted therapies.

Now, a multicenter team including researchers from Cleveland Clinic has shown that a combination of measurements within and outside a tumor on clinical dynamic contrast-enhanced magnetic resonance imaging is capable of discriminating the response-associated HER2-enriched (HER2-E) molecular subtype from other subtypes among patients with HER2+ tumors. (Current subtype identification requires costly gene expression profiling using tissue obtained by an invasive biopsy.)

When subsequently evaluated among recipients of HER2-targeted therapy, the new intratumoral and peritumoral imaging signature was found to be associated with response to neoadjuvant chemotherapy. The team's findings were published in the journal *JAMA Network Open*.

"Currently, if we see someone with a HER2-positive tumor, we always just give them chemotherapy and HER2-targeted medicine," says Jame Abraham, MD, Chair of Cleveland Clinic Taussig Cancer Institute's Department of Hematology and Medical Oncology, Director of the Breast Oncology Program and Co-Director of the Comprehensive Breast Cancer Program. "Until now, no one has looked at a predictive model to see who will benefit. This is the first use of radiology and radioanalysis to identify that subset of patients."

Potential treatment impacts

The approach uses computerized tissue phenotyping on radiographic imaging (radiomic) features extracted from breast MRI to examine the appearance of the tumor and its surroundings. A combination of local disorder, especially within the peritumoral environment, and larger-scale homogeneity near the tumor were found to most effectively characterize the treatment response-associated HER2-E molecular subtype.

LEFT: Imaging signature of treatment response-associated HER2-enriched molecular subtype.

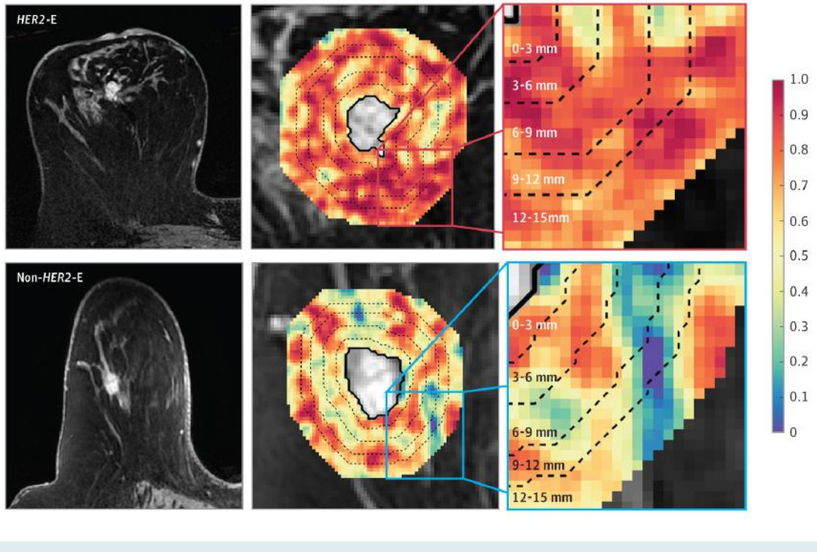


FIGURE 1. Co-occurrence of local anisotropy gradients (CoLIAGe) feature expression maps visualize the elevated disorder of local intensity gradient orientations within the peritumoral region of HER2-E relative to non–HER2-E breast cancers. Radiomic feature values are unitless, thus the scale depicts relative expression values of radiomic features, standardized between 0 and 1.0 based on the range of their distribution. The blue color at 0 depicts the minimum observed feature value; the red color at 1.0 depicts the maximum observed feature value.

Credit: Braman N, Prasanna P, Whitney J, et al. Association of Peritumoral Radiomics With Tumor Biology and Pathologic Response to Preoperative Targeted Therapy for HER2 (ERBB2)-Positive Breast Cancer. JAMA Netw Open. *2019 Apr 5;2(4):e192561.*

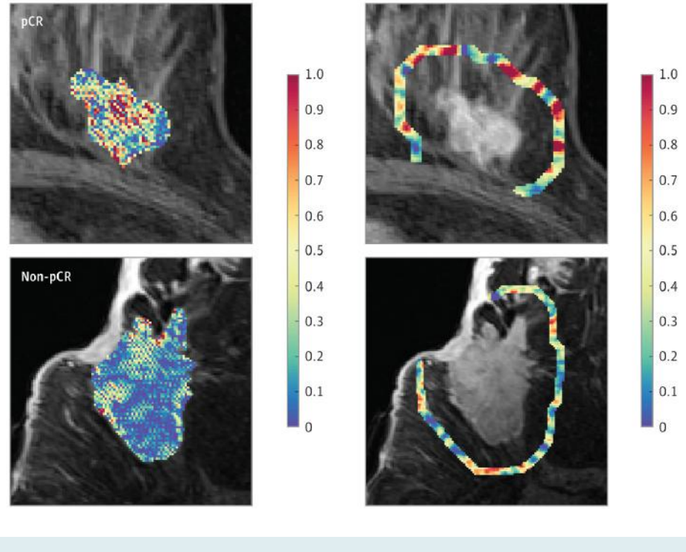


FIGURE 2. Imaging signature of HER2-E is associated with pathologic complete response to anti-HER2 therapy, with rippled enhancement patterns detected intratumorally by Laws feature (left), and elevated local peritumoral heterogeneity captured by CoLIAGe features 9 to 12 mm from the tumor (right) characterizing both features. Radiomic feature values are unitless, thus the scale depicts relative expression values of radiomic features, standardized between 0 and 1.0 based on the range of their distribution. The blue color at 0 depicts the minimum observed feature value; the red color at 1.0 depicts the maximum observed feature value.

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"We could potentially select patients upfront to treat with T-DM1. This would represent a major step for personalized medicine."

— JAME ABRAHAM, MD

If confirmed in subsequent studies, the technique could alter the course of treatment, since patients identified with nonresponsive HER2 molecular subtypes could be sent for surgical resection first and other treatments afterward, notes Abraham, who is also Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

Alternatively, this approach could be used to identify patients who might benefit from trastuzumab emtansine (T-DM1), an antibody-drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1), a maytansine derivative and microtubule inhibitor. In a landmark study published in December 2018, T-DM1 reduced the risk of recurrence of invasive breast cancer or death by 50% in patients with HER2+ early breast cancer who had residual invasive disease after completion of neoadjuvant therapy compared with trastuzumab alone.

"We could potentially select patients upfront to treat with T-DM1. This would represent a major step for personalized medicine," Dr. Abraham says.

Identifying responders radiographically

Initially, the investigators identified imaging features distinguishing HER2+ tumors from other receptor subtypes among 117 patients who received an MRI prior to neoadjuvant chemotherapy at a single institution between 2012 and 2015.

Then, using imaging and genomic data from a previous multicenter trial of 42 patients with HER2+ breast cancer and preoperative MRI and RNA sequencing data, they developed a signature to identify the HER2-E subtype among clinically HER2+ tumors. Previous radiomics studies have focused on analyzing the tumor itself, but the team found that adding information about its surroundings was critical to distinguishing HER2-E tumors.

To evaluate the utility of this signature in guiding treatment decisions, the team explored whether it could be used to predict targeted therapy outcome for HER2+ patients. When applied to a set of 78 patients from two institutions who had received MRI exams before HER2-targeted neoadjuvant chemotherapy, the signature was found to significantly identify patients who would achieve a complete response.

To better understand this signature, the researchers compared radiomic features with biopsy samples from the same patients. They observed that features from the 0-3 mm peritumoral region on MRI were significantly associated with the density of tumor-infiltrating lymphocytes on tissue samples — indicating a potential link between the way the immune system responds to a tumor and the appearance of its surroundings on imaging.

While the findings are compelling, Dr. Abraham cautions that "this is a completely experimental, retrospective study — a proof of concept. We need to validate this in larger datasets and confirm the data. Then we can potentially apply it more widely."

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Dr. Abraham is Chair of Cleveland Clinic Taussig Cancer Institute's Department of Hematology and Medical Oncology, Director of the Breast Oncology Program, Co-Director of the Comprehensive Breast Cancer Program and Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

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SHOULD WE RETHINK CANCER RISK STAGING IN FAMILIAL ADENOMATOUS POLYPOSIS?

Research suggests greater consideration for large polyp size, dysplasia

KEY POINTS

Spigelman stage (SS) IV polyposis traditionally has been a trigger for offering prophylactic duodenal surgery to prevent duodenal cancer in patients with familial adenomatous polyposis (FAP).

More than half of FAP patients diagnosed with duodenal cancer in a Cleveland Clinic case-control study lacked SS IV duodenal polyposis.

That inconsistency suggests certain individual characteristics of duodenal polyps in FAP patients have heightened significance in predicting cancer risk, irrespective of stage.

The formula for staging duodenal polyposis may need to be adjusted to give greater consideration to large polyp size and dysplasia, rather than focusing solely on the presence or absence of SS IV disease.

The presence of Spigelman stage (SS) IV duodenal polyposis is considered the most significant risk factor for duodenal cancer in patients with familial adenomatous polyposis (FAP).

But recent Cleveland Clinic research published in the journal *Gastrointestinal Endoscopy* highlights the inconsistency of SS as a cancer prediction risk indicator; more than half of FAP patients diagnosed with duodenal cancer in the case-control study lacked SS IV duodenal polyposis.

The results suggest that certain individual characteristics of duodenal polyps in FAP patients have heightened significance in predicting cancer risk, irrespective of stage, and that the formula for staging duodenal polyposis may need to be adjusted to take that into account, rather than focusing solely on the presence or absence of SS IV disease.

"Traditionally, SS IV polyposis has been a trigger for offering prophylactic duodenal surgery to prevent duodenal cancer in FAP," says study co-author Carol Burke, MD, Vice Chair of Cleveland Clinic Digestive Disease & Surgery Institute's Department of Gastroenterology, Hepatology and Nutrition, Director of the Center for Colon Polyp and Cancer Prevention, and Section Head of Polyposis in the Sanford R. Weiss, MD, Center for Hereditary Colorectal Neoplasia. "Our research shows that earlier SS patients with large or microscopically advanced polyps are also at high risk of cancer, and aggressive endoscopic intervention or duodenectomy should be considered if polyp burden cannot be controlled."

Dr. Burke and her colleagues believe their research is the first to examine individual SS components and papilla pathology in relation to duodenal cancer risk in FAP.

The pluses and minuses of Spigelman staging

FAP is an inherited colorectal cancer syndrome caused by a germline mutation in the *adenomatous polyposis coli* gene. Without colectomy, progression of colorectal polyposis to colorectal cancer is inevitable, usually by ages 40 to 50. The second leading cause of cancer in FAP is duodenal cancer, which arises from duodenal adenomatous polyposis and has an overall cumulative lifetime incidence of 4.5% by age 57.

The five-stage (0 to IV) SS system was developed 30 years ago to predict duodenal cancer risk and dictate the frequency of endoscopic surveillance and the timing of prophylactic duodenectomy. In calculating the SS score and stage, equal weight is assigned to each of the four polyp criteria — number, size, histology and degree of dysplasia.

Previous research showed FAP patients with SS IV polyposis had 10-year cumulative risk levels as high as 36% of developing duodenal cancer, versus 2.5% risk in patients with SS 0-III. But those data also showed that many FAP patients who developed cancers did not have SS IV polyposis.

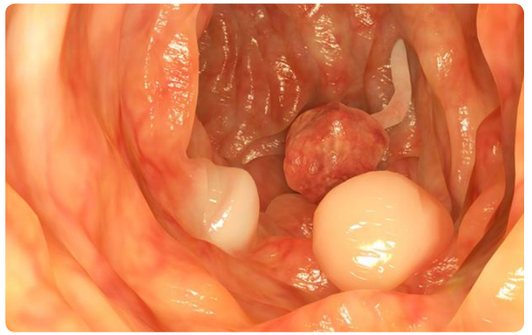
That variability of SS predictive accuracy is what prompted the Cleveland Clinic researchers to assess the relationship of SS and other factors with duodenal cancer in FAP.

Analyzing the data

The researchers queried the Cleveland Clinic hereditary colon cancer database for FAP patients with duodenal polyposis seen between 1988 and 2013. They identified 18 patients with duodenal cancer and, for comparison, randomly selected 85 similarly aged patients with FAP but without duodenal cancer. The researchers reviewed clinical data, including results of esophagogastroduodenoscopy performed on the cases and controls.

Statistical analysis found that SS IV polyposis was associated with duodenal cancer, but that 53% of patients with duodenal cancer had no prior SS IV polyposis — a considerably higher proportion than in previous research.

Regarding individual SS characteristics, duodenal polyps larger than 10 mm and polyps with high-grade dysplasia (HGD) were positively associated with cancer. Large polyps were present in 76.5% of cancer patients versus 47.1% of FAP patients without duodenal cancer (p = .027). Polyps with HGD were identified in 29.4% of cancer patients versus 5.9% of those without cancer (p = .003). The presence of more than 20 duodenal polyps and duodenal polyps with advanced histology (tubulovillous adenoma or villous adenoma) were not associated with cancer risk.



"The demonstration that not all SS characteristics have comparable predictive value for duodenal cancer begs the question of whether it is prudent to rethink the equal weighting of those components in risk stratification, instead giving greater consideration to large polyp size and dysplasia," Dr. Burke says.

The frequency of finding advanced pathology of the papilla with any villous features or HGD was greater in the cancer patients than in those without cancer (80% vs. 22% for villous features and 30% vs. 4% for HGD), regardless of whether the cancer was of the papilla/ampulla or elsewhere in the duodenum.

Spigelman classification for duodenal polyps in FAP

Criteria	Points		
	1	2	3
Polyp number	1-4	5-20	> 20
Polyp size (mm)	1-4	5-10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Stage 0 = 0 points; Stage I =1-4 points; Stage II = 5-6 points; Stage III = 7-8 points; Stage IV = 9-12 points

"There is no consensus on including endoscopic or histologic features of the duodenal papilla characterization in SS calculations," Dr. Burke says. "Our data support the importance of the histology of the papilla in assessing duodenal cancer risk and bolster the case for routine biopsy of the papilla and inclusion in SS."

The study also identified a personal and family history of colon cancer and the absence of desmoid tumors as characteristics in FAP patients developing duodenal cancer, which may be a function of the gene mutation causing the disease.

Clinical implications

Although larger studies are needed to validate the overall findings, reassessing the Spigelman staging system with a larger population should be considered, the authors conclude.

Meanwhile, Dr. Burke and her colleagues advocate regular duodenal polyposis surveillance, biopsy of the duodenal papilla and inclusion of histology findings of the papilla in the current SS. The presence of HGD, whether papillary or in the duodenum, should be a potential indicator of a high-risk patient and warrants close follow-up, the researchers say.

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Dr. Burke is Vice Chair of Cleveland Clinic Digestive Disease & Surgery Institute's Department of Gastroenterology, Hepatology and Nutrition; Director of the Center for Colon Polyp and Cancer Prevention; Section Head of Polyposis in the Sanford R. Weiss, MD, Center for Hereditary Colorectal Neoplasia; and Clinical Assistant Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

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CLEVELAND CLINIC FORMS CENTER FOR RESEARCH EXCELLENCE IN GYNECOLOGIC CANCER

Focus is on delivering advances most needed by patients

KEY POINTS

Cleveland Clinic's new Center for Research Excellence in Gynecologic Cancer is developing a comprehensive research program to translate basic science into clinical care.

The center will investigate a wide range of subjects, including genetic anomalies that confer radiation resistance in endometrial cancer, targeted immunotherapy for epithelial ovarian cancers, and the role of cancer stem cells in chemotherapy resistance.

The center will create a biorepository of patient tissue samples and establish patient-derived disease models for preclinical investigation of new therapies.

Gynecologic cancers, including endometrial and ovarian cancers, are a leading cause of cancer-related deaths in women. The ability of gynecologic tumors to adapt to and evade treatment is a major factor contributing to the poor outcomes that many patients face. The Center for Research Excellence in Gynecologic Cancer (CREGC) is a collaborative network for the development of a comprehensive research program to promote the translation of basic science investigation into the clinic.

The center's co-directors, Ofer Reizes, PhD, Department of Cardiovascular and Metabolic Sciences and the Cancer Impact Area, Lerner Research Institute, and Peter Rose, MD, Department of Gynecologic Oncology, Ob/Gyn & Women's Health Institute, believe the CREGC is exceptionally positioned to change the landscape of gynecologic cancer research and care.

The center will capitalize on the expertise and patient volume of Cleveland Clinic's Department of Gynecologic Oncology, which is recognized nationally by *U.S. News & World Report* for its clinical prowess. Additionally, Lerner Research Institute already has a portfolio of gynecologic cancer research underway.

Breakthrough research opportunities

Through core resources and an infrastructure designed to promote collaboration and accelerate translational medicine, the CREGC supports research projects that explore possible causes of and treatments for a range of gynecologic cancers, including:

- Characterizing genetic anomalies that confer radiation resistance in endometrial cancer.
- Identifying candidates for targeted immunotherapy to treat epithelial ovarian cancers.
- Developing therapies to overcome drug resistance in women with ovarian cancer who have the BRCA mutation.
- Determining the role cancer stem cells and related molecules play in chemotherapy resistance.

"We are really driving research at the bench to care at the bedside, ensuring that our research informs clinical care and vice versa," states Dr. Reizes. "Our aim is to create tangible benefits for patients by bringing together lab scientists with front-line physicians to focus on the advances most needed by patients, now."

In addition to supporting specific research projects, the CREGC will help drive research and cures by developing a shared biorepository of patient samples and establishing patient-derived disease models for preclinical investigation of new therapies. In 2018, the CREGC established and successfully executed a process for engrafting primary tumors for future testing. In the coming months, the group will focus on expanding its tissue and specimen collection and explore the utilization of patient-derived xenograft models in clinical practice.

LEFT: Peter Rose, MD

"Opportunities for breakthroughs in gynecologic cancer are in the team we've built," Dr. Reizes says. "Bringing together a multidisciplinary team to focus on this problem makes me hopeful that we will move the needle on these diseases."

Ensuring the best possible patient outcomes

In addition to the CREGC's efforts, Cleveland Clinic's Gynecologic Oncology Cancer Program offers patients the latest in gynecologic cancer management, including the newest drug therapies.

"As part of NRG Oncology, an international cooperative research group funded by the National Cancer Institute and National Institutes of Health, we can offer patients who qualify access to investigational treatments through a wide range of clinical trials," states Dr. Rose. "Additional studies give eligible patients access to other new treatments under investigation in the CREGC, such as hyperthermic intraperitoneal chemotherapy, or HIPEC."

The Gynecologic Oncology Cancer Program also offers minimally invasive surgery, sophisticated radiation therapy techniques and specialized imaging.

"Our team of highly trained specialists — including gynecologic pathologists, radiation oncologists, nurse practitioners, physician assistants, nurse navigators, chemotherapy coordinators, genetic counselors and social workers — works with patients to provide precise diagnosis, exacting surgical skill and leading-edge therapies," Dr. Rose notes. "Throughout the entire patient experience, we emphasize comfort and empathy."

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Dr. Reizes holds the Laura J. Fogarty Endowed Chair for Uterine Cancer Research and is a staff member of Cleveland Clinic Lerner Research Institute's Department of Cardiovascular and Metabolic Sciences, the Department of Cellular and Molecular Medicine, and the Cancer Impact Area. He is Assistant Professor of Molecular Medicine at Cleveland Clinic's Lerner College of Medicine.

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Dr. Rose is Section Head and Fellowship Director of Gynecologic Oncology in the Ob/Gyn & Women's Health Institute's Department of Obstetrics and Gynecology, and Professor of Surgery at Cleveland Clinic Lerner College of Medicine.

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REAFFIRMING THE OPTIMAL TOTAL DOSE OF CISPLATIN FOR HIGH-RISK ORAL CAVITY SQUAMOUS CELL CARCINOMA

It nearly doubles median disease-free survival

KEY POINTS

Cisplatin and radiotherapy following tumor resection is the standard of care in patients with high-risk oral cavity squamous cell carcinoma (OCSCC).

Since high-dose cisplatin is extremely toxic and difficult to tolerate, identifying the dosage with the best efficacy and least toxicity is important.

A Cleveland Clinic-led retrospective study evaluating alternative cisplatin dosing schedules for high-risk OCSCC patients reaffirmed a previously suggested optimal total cisplatin dose of 200 mg/m^2 or more.

Patients who received this dose had nearly double the median disease-free survival of patients who received less. There was no significant difference in disease-free survival among patients who received cisplatin as a bolus and those who received weekly dosing.

In oral cavity squamous cell carcinoma (OCSCC), the standard of care is resection. In high-risk cases — those identified by positive surgical margins and extranodal extension — resection is followed by radiation therapy and intravenous cisplatin.

However, high-dose cisplatin is extremely toxic and difficult for patients to tolerate. It is highly emetogenic, nephrotoxic and ototoxic, and patients often experience additional side effects common with chemotherapy, including myelosuppression and peripheral neuropathy.

These adverse effects are compounded by those caused by radiation therapy to the head and neck. For example, mucositis often causes dysphagia and odynophagia, which can lead to malnutrition, necessitating alternative means of obtaining enteral nutrition.

"Regarding toxicities and side effects, I explain to my patients that adding chemotherapy to radiation can be a 1 + 1 = 10 situation," says Cleveland Clinic oncologist Jessica Geiger, MD.

High dose vs. weekly cisplatin dosing

Identifying therapies and administration schedules with the best effectiveness and least toxicity is always the goal, she notes.

To this end, Dr. Geiger and a multi-institutional team established a large database of patients treated for OCSCC. Patients were treated at one of six academic institutions:

- Cleveland Clinic's Taussig Cancer Institute.
- Lee Moffitt Cancer Center & Research Institute.
- Henry Ford Health System.
- Memorial Sloan Kettering Cancer Center.
- Princess Alexandra Hospital (Australia).
- University of Louisville Hospital.

With nearly 1,300 patients, the Institutional Review Board-approved multi-institutional database is one of the largest cohorts for OCSCC, says Dr. Geiger. Many studies have mined the extensive, long-term data for survival and toxicity statistics.

Most recently, Dr. Geiger led a retrospective study evaluating alternative cisplatin dosing schedules.

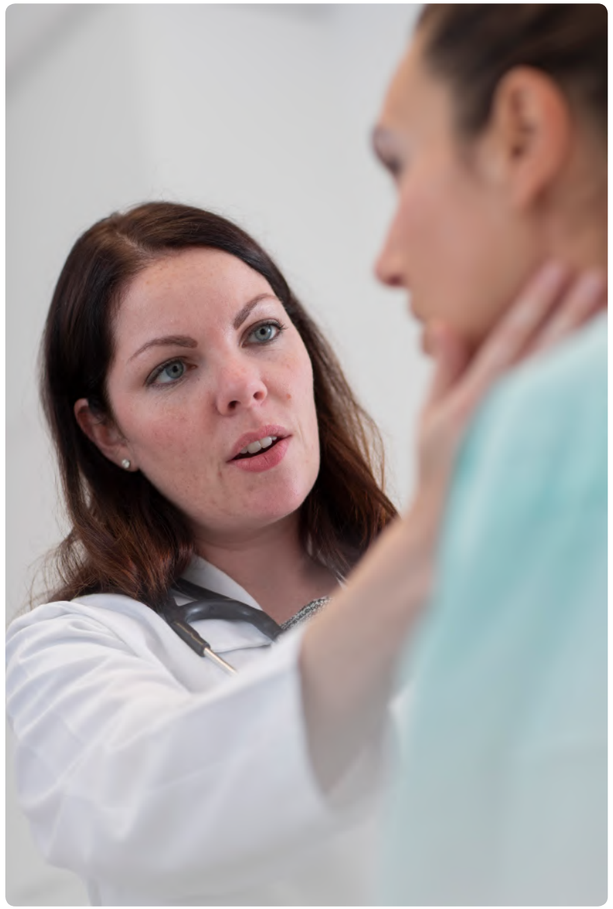
"We weren't able to discern whether administering cisplatin in a high-dose bolus or in weekly cumulative doses affected survival end points," says Dr. Geiger. "But we did reaffirm an optimal total dose that had been suggested previously in the literature."

Dr. Geiger presented results of the study at the 2019 American Society of Clinical Oncology Annual Meeting.

Optimal total dose: at least 200 mg/m^2

For this study, a subset of 196 patients met inclusion criteria:

- Treated for OCSCC between 2005 and 2015.
- Had positive surgical margins (35.7%) and/or extranodal extension (82.7%) following resection.
- Treated concurrently with radiation therapy and chemotherapy.



LEFT: Jessica Geiger, MD

Of these patients:

- Median age was 56.
- 3% were men.
- 1% were Caucasian.
- 9% had significant tobacco history.

"Looking retrospectively at this cohort, we learned that patients who received 200 mg/m^2 or more of cisplatin had nearly double the median disease-free survival of patients who received less," says Dr. Geiger.

Median disease-free survival was:

- Five months in patients who received less than 200 mg/m^2 of cisplatin.
- Eight months in patients who received 200 mg/m^2 or more of cisplatin.

There was no significant difference in disease-free survival among patients who received cisplatin as a bolus and those who received weekly dosing.

Univariate analysis also showed associations between higher doses of cisplatin and improved locoregional control (p = .131), metastatic disease (p = .084) and overall survival (p = .187). However, none of these associations was statistically significant, notes Dr. Geiger.

Administration options

"This study reaffirms that patients with high-risk resected OCSCC require systemic therapy with cisplatin and need to receive as much of it as possible during the course of radiation therapy," says Dr. Geiger. "There is a distinct benefit when patients get at least 200 mg/m^2, whether in a bolus or weekly dosing."

A prospective study is needed to evaluate different cisplatin dosing schedules and determine the optimal administration for high-risk OCSCC patients.

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Dr. Geiger is a staff member of Cleveland Clinic Taussig Cancer Institute's Department of Hematology and Medical Oncology and Assistant Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

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INOTUZUMAB OZOGAMICIN PROVES SUPERIOR TO STANDARD CHEMOTHERAPY FOR RELAPSED/REFRACTORY ALL IN A LONG-TERM FOLLOW-UP STUDY

Two-year follow-up confirms initial findings of the INO-VATE trial

KEY POINTS

A long-term follow-up study has verified the superiority of inotuzumab ozogamicin (INO) to standard chemotherapy for relapsed/refractory acute lymphoblastic leukemia.

INO produced higher rates of complete remission and longer median overall survival, but showed a greater incidence of veno-occlusive disease (VOD).

39.6% of patients who received INO achieved remission and minimal residual disease negativity and went on to hematopoietic stem cell transplant, versus 10.5% who were treated with standard-of-care chemotherapy.

Researchers are now examining whether the heightened VOD risk can be reduced with prophylactic medications prior to transplant or by reducing the dose of INO and combining it with other agents.

The promising preliminary survival and remission outcomes that inotuzumab ozogamicin (INO) produced in relapsed or refractory acute lymphoblastic leukemia (ALL) patients in the antibody-drug conjugate's phase 3 trial have been sustained in a long-term follow-up study.

The final report of the INO-VATE (INotuzumab Ozogamicin trial to inVestigAte Tolerability and Efficacy) trial, published in the journal *Cancer*, found that INO generated greater rates of complete remission (CR) and longer median overall survival (OS), but showed a greater incidence of veno-occlusive disease (VOD), compared with results in ALL patients treated with standard-of-care chemotherapy.

"INO is a very encouraging drug in the setting of relapsed/refractory ALL, and this long-term follow-up study has validated its OS advantage," says study co-author Anjali Advani, MD, Director of Cleveland Clinic Taussig Cancer Institute's Inpatient Leukemia Program. "The main challenge we still have to deal with is the risk of VOD, but INO definitely has an advantage in patients with high tumor burden or extramedullary disease. I also tend to favor it in patients with central nervous system disease, because it can be given with concurrent intrathecal chemotherapy."

The original INO-VATE trial assessed the safety and efficacy of single-agent INO compared with standard chemotherapy in relapsed/refractory ALL. INO is a humanized monoclonal antibody drug conjugate that binds to CD22+ ALL cells. The antibody is conjugated to calicheamicin, a cytotoxic compound that causes DNA damage and apoptosis.

INO-VATE's results led the Food and Drug Administration to approve the drug's use in adults with relapsed or refractory B-cell precursor ALL.

Challenging VOD rates

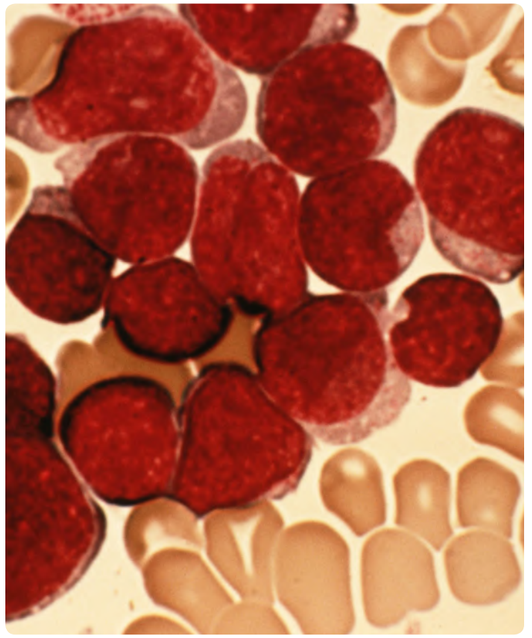
The main purpose of the follow-up study was to assess whether INO is superior to the standard-of-care chemotherapy over a period of two years.

"We looked at the response/complete remission rates, toxicity, OS, disease-free survival, minimal residual disease (MRD) negativity and the percentage of patients who were able to go on to [hematopoietic stem cell] transplant," says Dr. Advani.

The two-year follow-up largely confirmed the initial findings of the INO-VATE trial, with even more impressive outcomes in terms of OS and the percentage of patients who achieved MRD negativity and proceeded to transplant.

"The difference in the OS in patients who received INO (22.8%) compared with those who received standard chemotherapy (10%) has become more pronounced after the two-year follow-up," she says. "The outcome of patients who proceeded to transplant is even more impressive in the subgroup who received INO and went into remission, achieved MRD negativity and went on to transplant (39.6% INO vs. 10.5% standard of care)."

Medical Images RM



LEFT: Photomicrograph of ALL bone marrow showing small, medium and large hemoblasts.

However, the risk of VOD in patients who are transplanted remains a concern, she notes. VOD/sinusoidal obstruction syndrome was significantly more frequent in the INO arm (14%) compared with the standard-of-care arm (2.1%).

"We are now looking at how we can decrease that toxicity by either giving these patients medications (i.e., defibrotide) prophylactically prior to transplant or reducing the dose of INO and combining it with other agents," says Dr. Advani.

In both treatment arms, the most frequent all-grade and grade 3 or higher adverse events were hematologic.

"Hematologic events are very common with both INO and the standard-of-care chemotherapy," she says. "But the neutropenia, thrombocytopenia and anemia we saw were fairly easily managed. For those patients who are not going on to transplant and are receiving multiple cycles, the low platelet count can become an issue."

Next research steps

In terms of continuing research on INO, Dr. Advani says upfront use of the drug is currently being investigated in several clinical trials. In the ALLIANCE (A041501) trial, led by Daniel J. DeAngelo, MD, PhD, of the Dana Farber Cancer Institute, INO is being evaluated in combination with chemotherapy in young adults with newly diagnosed CD22+ B-cell acute lymphoblastic leukemia.

"The question we are trying to answer in this trial is, if we use the drug in the upfront setting, will we have better outcomes, fewer relapses and maybe lower toxicity, because those patients hopefully won't be going on to transplant," explains Dr. Advani, who is one of the study's principal investigators.

A second planned U.S. intergroup trial led by Elias Jabbour, MD, of the University of Texas MD Anderson Cancer Center, will randomize elderly patients with ALL to either mini-hyper-CVD (low-intensity chemotherapy) or mini-hyper-CVD plus INO.

A third trial (S1312) that has completed accrual is reviewing INO plus chemotherapy (cyclophosphamide, vincristine sulfate and prednisone [CVP]) in patients with relapsed or refractory CD22+ acute leukemia. This is a Southwest Oncology Group trial in which Dr. Advani serves as a principal investigator.

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Dr. Advani is Director of Cleveland Clinic Taussig Cancer Institute's Inpatient Leukemia Program, a staff member of the Department of Hematology and Medical Oncology and Department of Translational Hematology and Oncology Research, and Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

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SURGERY OPENS NEW POSSIBILITIES FOR TREATING LIVER METASTASES FROM COLORECTAL CANCER

Two-stage procedure capitalizes on liver's ability to regenerate

KEY POINTS

A novel two-stage surgery offered at Cleveland Clinic, known as associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), makes it possible to treat patients with liver metastases from colorectal cancer who don't qualify for traditional liver resection due to multicentric disease and an inadequately small future liver remnant.

In the first stage, hepatobiliary surgeons excise tumors in the lesser-affected liver lobe, ligate the portal vein supplying blood to the other lobe and partition the liver to interrupt intrahepatic vascular connections.

This simultaneously enhances growth of the now tumor-free lobe while shrinking the contralateral lobe with the greater tumor burden, which will be resected during a follow-up procedure.

With careful application, ALPPS can improve survival in patients who have no alternative treatments.

An innovative surgical treatment option that leverages the liver's regenerative capacity is showing promise for some patients with previously unresectable liver metastases from colorectal cancer.

The two-stage surgery, known as associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), makes it possible to treat patients who are not appropriate candidates for traditional liver resection due to multicentric disease and an inadequately small future liver remnant.

When both lobes contain tumors, hepatobiliary surgeons and radiologists in Cleveland Clinic Digestive Disease & Surgery Institute's Liver Tumor Cancer Program work together to identify the lobe with the lower tumor burden. After excising the lesions in this lesser-affected lobe, the true novelty of their approach begins. They simultaneously enhance the growth of this lobe while working to shrink the contralateral lobe — the one with the greater tumor burden — so that it can be more easily resected during a follow-up procedure.

"The ALPPS procedure allows us to treat patients who have a substantial amount of tumor, with both lobes affected by tumor," says Federico Aucejo, MD, Director of the Liver Cancer Program, Surgical Director of the Liver Tumor Clinic and Co-Director of the Liver Tumor Center of Excellence.

In the first stage of ALPPS surgery, at the same time that surgeons resect the metastases from one lobe, they ligate the portal vein supplying blood to the other. They also partition the liver with a transecting incision of the parenchyma to interrupt intrahepatic vascular connections. This approach serves a dual purpose — starving the metastatic hemi-liver of its blood supply while diverting as much as possible to the lobe that will be preserved.

Partitioning the liver helps enhance growth of the future liver remnant by stimulating increased expression of growth factors and cytokines and inducing hyperplasia, Dr. Aucejo explains. "This not only makes the lobe of the liver grow larger, but does it faster."

"We can then perform the second and larger operation, where we remove the contralateral side — the lobe with the greater tumor burden," he says. The second stage typically is performed one to two weeks after the first operation.

Embolization and venous deprivation approaches

Portal vein embolization is another method to convert unresectable bilobar cancer into resectable by inducing hypertrophy of liver segments. Following excision of the small metastatic lesions in the future liver remnant, rather than performing surgical ligation of the portal vein, interventional radiologists perform perioperative embolization (using a percutaneous catheter to deliver embolic agents to occlude the vein), redirecting portal blood to the future liver remnant.

LEFT: Federico Aucejo, MD

FIGURE 1. Preoperative computed tomography (CT) shows extensive bilobar liver metastases from colorectal cancer.

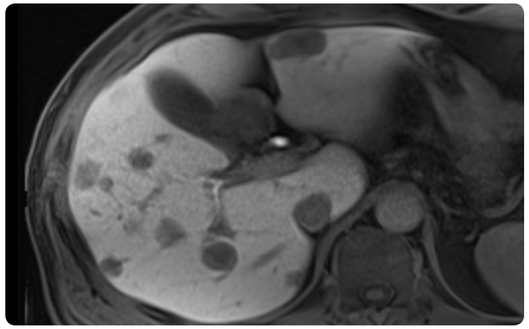
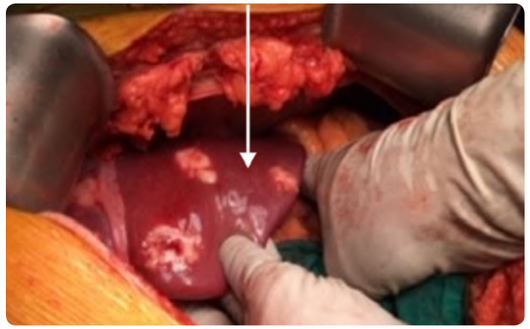


FIGURE 2. First-stage hepatectomy to clear metastases from the left lateral segment.



A distinct advantage of occlusion is less manipulation of the local anatomy. "When we come back for the second stage of the procedure, we find virgin tissue there," Dr. Aucejo says. "Generally, there is less inflammation, and dissection of the tissue is easier."

Interventional radiologists also can perform a venous deprivation technique. In addition to cutting off the blood flow to half the liver, they embolize the hepatic vein coming out of the same lobe. "That allows for substantial atrophy of that lobe and substantial growth of the contralateral lobe, the one that we are going to leave in the patient," Dr. Aucejo says.

The importance of careful patient selection

Physicians in the Liver Tumor Cancer Program have performed about 10 ALPPS and venous embolization/deprivation procedures to date. Whichever approach is used, preserving at least 30% of total liver volume is the mandatory safety margin. In terms of patient selection, patients 60 years old or younger generally have better outcomes with these two-stage interventions.

"This surgical technique is applied in very select patients," Dr. Aucejo says. "But it clearly opens an opportunity for improved patient survival when there are no other alternatives."

For example, recently an out-of-state colorectal cancer patient with extensive bilobar metastases that were not amenable to traditional resection sought a consult with Cleveland Clinic. "After evaluating the liver volumetry and tumor burden affecting both lobes, I decided to offer an ALPPS procedure, as it was the best possible option to clear the liver of disease," Dr. Aucejo says.

Months after surgery, the patient developed a small recurrence in the remaining liver, which was treated with external beam radiation. "As of today, the patient is back in his hometown, reconnecting with his normal life and family," Dr. Aucejo says.

An extensive toolkit

Cleveland Clinic is one of the few centers offering a comprehensive range of advanced techniques to treat complex liver cancer cases.

They require "a high level of surgical expertise," Dr. Aucejo says. "ALPPS is a valuable part of a comprehensive toolkit we have to treat these patients, which includes systemic treatment, surgical therapies and interventional radiology strategies. Despite the evolution of nonsurgical treatments when surgical options are not possible, five-year survival ranges between 10% and 20%, as opposed to 30% to 60% when surgery can be performed."

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Dr. Aucejo is Director of Cleveland Clinic Digestive Disease & Surgery Institute's Liver Cancer Program, Surgical Director of the Liver Tumor Clinic, Co-Director of the Liver Tumor Center of Excellence, and Associate Professor of Surgery at Cleveland Clinic Lerner College of Medicine.

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On Twitter: @FAucejo

FIGURE 3. First-stage hepatectomy showing left lateral segment after metastases resection.

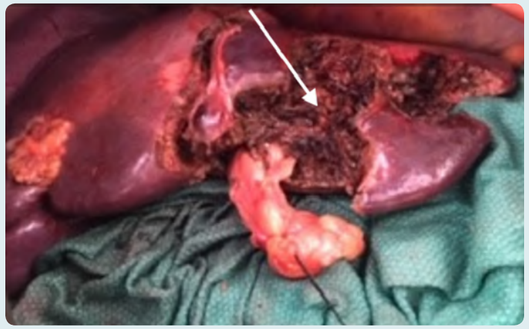


FIGURE 4. First-stage hepatectomy showing ligation of right anterior and right posterior portal veins.

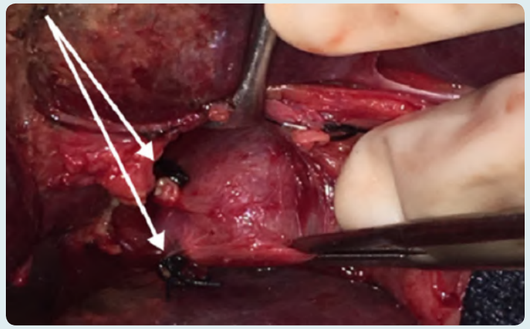


FIGURE 5. First-stage hepatectomy showing transection of the liver.

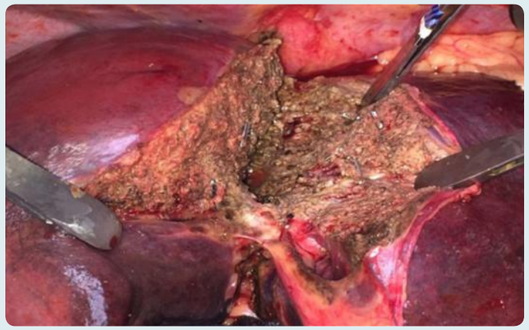


FIGURE 6. Second-stage (extended right) hepatectomy.

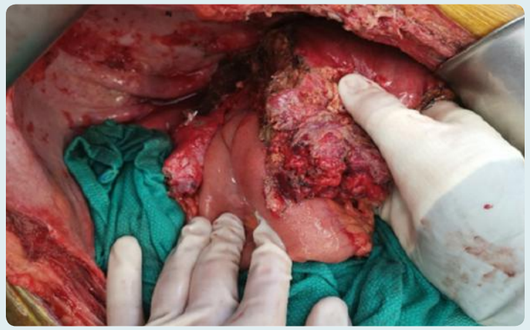


FIGURE 7. Resected extended right lobe.

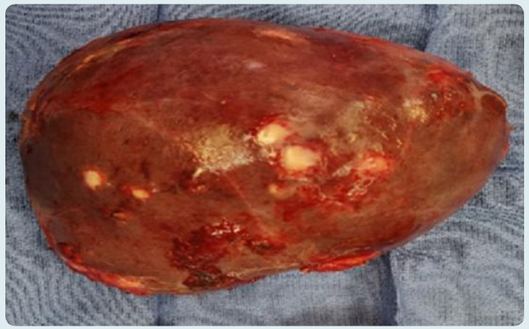
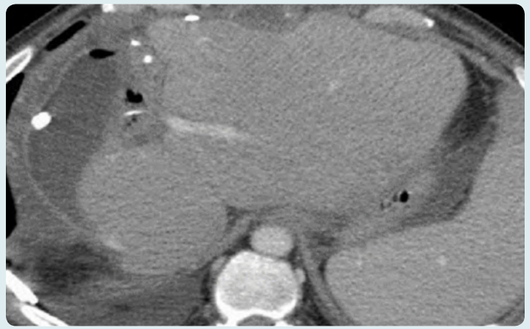


FIGURE 8. CT scan after second-stage hepatectomy, showing enlarged left lateral segment without radiologic evidence of tumor.



LOW CD30 EXPRESSION IN NON-HODGKIN'S LYMPHOMA PATIENTS DOES NOT PREDICT LOW RESPONSE TO BRENTUXIMAB VEDOTIN

RIGHT: Deepa Jagadeesh, MD

LOW CD30 EXPRESSION IN NON-HODGKIN'S LYMPHOMA PATIENTS DOES NOT PREDICT LOW RESPONSE TO BRENTUXIMAB VEDOTIN

Study raises questions about association between expression level and efficacy

KEY POINTS

The membrane protein CD30's prevalence in multiple types of lymphoma cells has made it a chemotherapy target.

Previous research established the efficacy of the anti-CD30 antibody drug conjugate brentuximab vedotin (BV) in treating CD30-positive peripheral T-cell lymphoma subtypes, but did not examine whether patients with low (< 10%) CD30 expression levels were responsive to BV.

Cleveland Clinic researchers analyzed data from T- and B-cell lymphoma patients with low to undetectable CD30 expression levels and identified BV responsiveness, some of it durable.

Variability of CD30 expression within a patient's biopsy samples or lack of sensitivity in CD30 expression assays may explain BV's clinical activity in patients with low CD30 expression levels.

The ECHELON-2 trial, published in 2018, helped establish the efficacy of brentuximab vedotin (BV), in combination with chemotherapy, for treating CD30-positive peripheral T-cell lymphoma subtypes.

The results of a new study, presented at the American Society of Clinical Oncology's 2019 annual meeting, invite questions about the association between the efficacy of BV, an anti-CD30 antibody drug conjugate, and the level of CD30 expression.

Deepa Jagadeesh, MD, first author of the study, is a Cleveland Clinic oncologist and assistant professor at Cleveland Clinic Lerner College of Medicine. She presented her team's findings that having CD30 levels that are < 10% or absent, as detected through immunohistochemistry (IHC) stain, did not predict patients' objective response to BV.

CD30 is a membrane protein of the tumor necrosis factor receptor family, and it plays a role in cell proliferation and apoptosis. While it can be expressed in healthy cells, its prevalence in multiple types of lymphoma cells has rendered it a chemotherapy target.

BV works by becoming internalized in the cell after binding to CD30, causing cell death. It is approved in the relapsed setting for Hodgkin's lymphoma, CD30-positive cutaneous T-cell lymphoma (CTCL) and systemic anaplastic large cell lymphoma. In late 2018 it was also approved for upfront treatment of CD30-positive peripheral T-cell lymphoma (PTCL), in combination with chemotherapy, based on ECHELON-2 results.

No predictive correlation

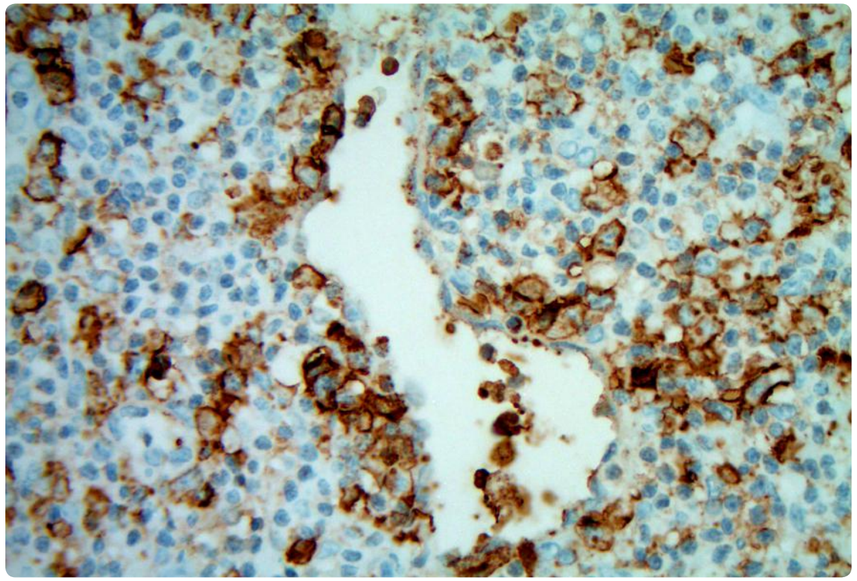
Since patients with CD30 expression of < 10% were not included in the ECHELON-2 trial, this study sought to find out whether this particular subgroup responded to BV. To do this, the researchers analyzed data on 275 patients from five different studies on T-cell and B-cell lymphomas.

A total of 140 of these patients had tumors with CD30 expression of < 10%, including 60 with undetectable expression. Findings showed that patients with PTCL, CTCL and B-cell lymphoma with low/undetectable CD30 expression responded to BV.

"It's intriguing to see responses even in patients with zero CD30 expression, and some of the responses are durable," says Dr. Jagadeesh.

Digging deeper for explanations

Dr. Jagadeesh points to several evidence-based hypotheses that might explain the clinical activity seen in these patients who have low or no detected CD30 expression. One is that the current method for detecting CD30 by IHC stain may not be sensitive enough to detect all the cells expressing this marker. Another possible explanation is that there could be intrapatient variability in CD30 expression within biopsy samples.



LEFT: CD30 staining in non-Hodgkin's lymphoma.

"It's intriguing to see responses even in patients with zero CD30 expression, and some of the responses are durable."

— DEEPA JAGADEESH, MD

An ongoing phase II clinical trial at Cleveland Clinic is seeking to determine the best method to measure CD30 expression and to identify the patient population that may benefit from this treatment.

T-cell lymphoma is a rare heterogeneous disease compared with B-cell lymphoma, comprising only 15% of non-Hodgkin's lymphoma cases. Prognosis is poor in this entity as the overall survival rates are around 30%-35% for the most common subtypes and 5%-10% in some of the rarer subtypes.

"Because it is rarer, there is much less research related to T-cell lymphoma than to B-cell, so our knowledge about the disease biology is sparse," says Dr. Jagadeesh.

She and her study team will be further reviewing the data to better understand the relationship between CD30 expression and clinical response to BV. Ideally, ongoing research efforts will continue to identify novel agents that are active in T-cell lymphoma, and studies evaluating combination therapies will help improve outcomes for patients with this disease.

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Dr. Jagadeesh is a staff member of Cleveland Clinic Taussig Cancer Institute's Department of Hematology and Medical Oncology and Clinical Assistant Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

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TRENDS IN STEREOTACTIC LASER ABLATION FOR BRAIN TUMORS: MOUNTING EXPERIENCE AND ENHANCED TECHNOLOGY ARE BOOSTING OUTCOMES

Insights from 240 cases over eight years at Cleveland Clinic

KEY POINTS

Cleveland Clinic's growing experience with stereotactic laser ablation for brain tumors and the deployment of next-generation devices helped drive dramatic improvements in operative times and outcomes between 2011 and 2018, according to a retrospective case review.

The predominant tumor types treated with stereotactic laser ablation shifted from upfront and recurrent gliomas to metastases and radiation necrosis following radiosurgery failure.

Operative time was reduced by almost half during the study period. The rate of permanent postoperative complications fell to 4%, and postoperative mortality declined to 1.5%.

Outcomes and operative times associated with stereotactic laser ablation for treating brain tumors dramatically improved over the past eight years at a single institution even as the procedure was increasingly used to treat metastases and radiation necrosis from radiosurgery failure.

These findings — from a retrospective review of 240 Cleveland Clinic patients since 2011 — were detailed in a platform presentation at the 2019 annual scientific meeting of the American Association of Neurological Surgeons.

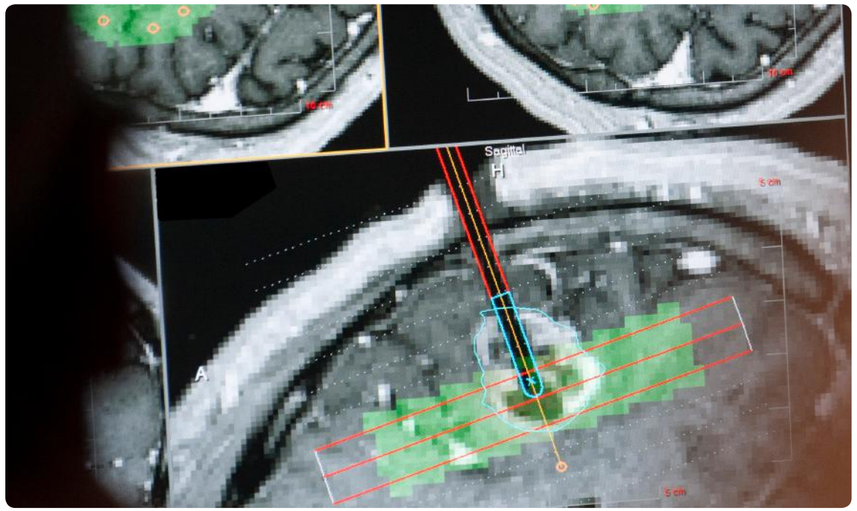
"Cleveland Clinic was one of the early adopters of stereotactic laser ablation treatment for brain tumors, so we have good data starting in 2011, when the technology became commercially available after FDA approval," says the study's principal investigator, Alireza M. Mohammadi, MD, a neurosurgeon with Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center. "Assessing our experience allows us to detect important trends and develop evidence-based best practices for other centers with more limited experience to follow."

Study design and findings

The study categorized patients into two time periods for comparison: the early period, from 2011 to 2014 (102 patients), and the more recent period, from 2015 to 2018 (138 patients). Extensive data on patient demographics, surgical and tumor characteristics, and temporary and permanent complications (the latter defined as unresolved after six months) were assessed.

The following differences were detected between the early and recent periods:

- Tumor types changed. In the early years, stereotactic laser ablation was predominantly used for upfront and recurrent gliomas (76.6%). Over time, utilization markedly increased for treating metastases and radiation necrosis following radiosurgery failure, changing from 25 combined cases (23.4%) in the early years to 58 cases (42.6%) in recent years.
- Operative time shortened, from 6.25 hours in the early years to 3.6 hours in recent years.
- Complication rates improved. Rates of permanent postoperative deficits declined from 15% to 4%, a significant change. Dr. Mohammadi says this decline was likely due in part to modification of the team's surgical techniques, following review of the initial series of cases, to protect eloquent brain area close to the tumor and laser field (*Neurosurg Focus.* 2016;41:E11). "Additionally, there were no cases of infection or large hemorrhage needing surgery in the second cohort," he notes.
- Postoperative mortality and severe morbidity decreased. Mortality improved from 4.2% in the early group to 1.5% in the recent period.



LEFT: MRI-guided stereotactic laser ablation using the NeuroBlate system.

Dr. Mohammadi credits these substantial changes over the years to growing experience on the part of the multidisciplinary team as well as evolving technology. In 2013, a new generation of the stereotactic laser ablation device (NeuroBlate® System) became available, allowing more efficient delivery of energy from the laser probe as well as improved planning and placement of the laser probe into the tumor.

Most common applications

Stereotactic laser ablation is a powerful tool that plays an increasing role in treating challenging brain tumors and their complications, Dr. Mohammadi notes. Some of the most important evolving applications include:

- Radiation necrosis. Radiation necrosis is a frequent complication of radiosurgery for brain metastases, occurring in about 10% to 15% of cases, often causing neurological deterioration. A multicenter study led by Cleveland Clinic (*J Neurosurg.* 2018;130:804-811) found that stereotactic laser ablation offers good control for radiation necrosis, resulting in stabilized performance and preserved quality of life and cognition.
- High-grade gliomas. Complete resection of difficult-to-access high-grade gliomas is rarely achievable surgically, according to Dr. Mohammadi, who co-authored studies assessing the role of stereotactic laser ablation for these tumors (*Cancer Med.* 2014;3:971-979; and *Neurosurgery.* 2018 Sep 1;83(3):556-565. Laser ablation was shown to be safe and effective in this setting.

"We now have enough evidence to confidently say that stereotactic laser ablation can fill important roles for treating primary and metastatic brain tumors and radiation necrosis," says Dr. Mohammadi. "We expect its uses to continue to evolve as technology advances, further enhancing our capabilities."

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Dr. Mohammadi is a staff member of Cleveland Clinic Neurological Institute's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center and Assistant Professor of Neurological Surgery at Cleveland Clinic Lerner College of Medicine.

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POST-PROSTATECTOMY PROSTATE-SPECIFIC ANTIGEN KINETICS ASSOCIATED WITH RECURRENCE AFTER SALVAGE RADIATION

Relapse more likely with faster PSA doubling time

KEY POINTS

The latest update to a nomogram widely used to predict prostate cancer mortality after salvage radiotherapy (SRT) adds prostate-specific antigen (PSA) kinetics to the predictive factors.

The addition of initial postoperative PSA level and PSA doubling time is the result of a Cleveland Clinic-led analysis of PSA kinetic data from 1,005 post-prostatectomy patients.

That review found that an initial postoperative PSA ≥ 0.5 ng/mL is significantly associated with risk of biochemical failure, and PSA doubling time < 6 months is significantly associated with increased rates of biochemical failure and distant metastases.

The incorporation of PSA kinetics in the nomogram provides a more precise estimation of potential outcomes following SRT.

The integration of prostate-specific antigen (PSA) kinetics into a nomogram widely used to predict outcomes of salvage therapy offers physicians and patients a more nuanced, longer-term look at prostate cancer-specific outcomes.

In 2007, a multi-institutional cohort led by Cleveland Clinic's Glickman Urological & Kidney Institute developed a nomogram to predict prostate cancer-specific and all-cause mortality at six years after salvage radiotherapy (SRT).

Almost a decade later, a study led by Cleveland Clinic Cancer Center radiation oncologist Rahul D. Tendulkar, MD, updated the nomogram with evidence that early initiation of SRT following radical prostatectomy reduced biochemical failure (BF) and distant metastases (DM).

The researchers' most recent update to the nomogram was presented at the 2019 annual meeting of the American Society for Radiation Oncology (ASTRO).

"One critique of our previous update was the lack of PSA kinetics among the predictive factors," says Shauna Campbell, DO, Chief Resident, radiation oncology, Cleveland Clinic. "This version of the nomogram adds initial postoperative PSA level and PSA doubling time [PSADT] to the picture."

Refining the data

Early versions of the nomogram included patients from 10 consortium institutions, in many of whom researchers could not accurately estimate PSADT. For this study, the team narrowed the data to 1,005 patients from five institutions with available PSA kinetic data, and were able to calculate PSADT from 662 of them. Study subjects had node-negative prostate cancer with median pre-SRT PSA levels of 0.4 ng/mL, with a median follow-up of five years.

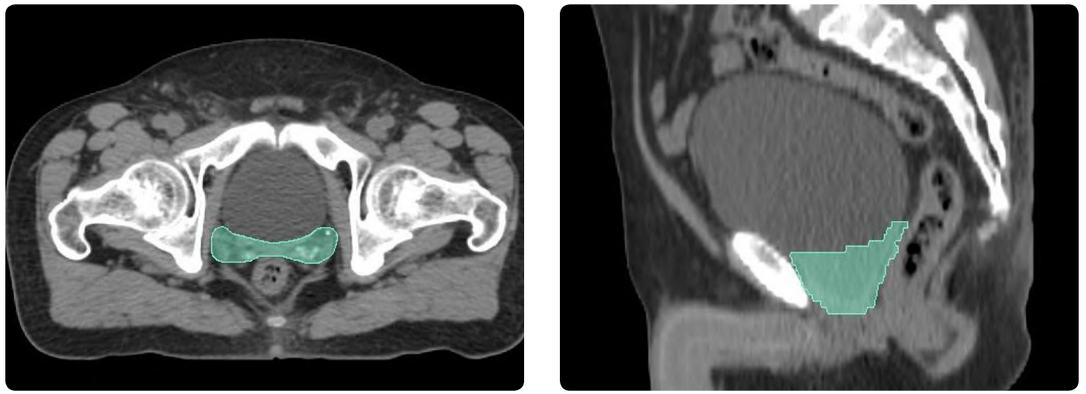
The team performed multivariable analyses (MVA) by Cox proportional hazards regression to pinpoint risk factors for DM and BF (defined as post-SRT PSA > 0.2 ng/mL). Most subjects had a Gleason score (GS) of 7 (n = 632, 63%), with 20% having GS 6 (n = 197) and 9% each with GS 8 (n = 86) and GS 9-10 (n = 90). Fifty-four percent of subjects had extraprostatic extension, and 19% had seminal vesicle invasion (SVI). Margins were positive in 59%. Thirteen percent received concurrent androgen deprivation therapy (ADT), 46% were treated with ≥ 66 Gy and 20% received pelvic RT.

Impact of PSA kinetics

MVA showed that pre-SRT PSA and PSADT were significantly associated with BF, along with GS, surgical margins, use of ADT, RT dose ≥ 66 Gy, pelvic nodal RT and SVI.

PSADT and pre-SRT PSA were also significantly associated with DM, in addition to GS, surgical margins, SVI and pelvic nodal RT. Specifically, PSADT of less than six months was significantly

BELOW: Axial and sagittal computed tomography images of the post-prostatectomy clinical target volume (delineated in aqua) for salvage radiation planning.



associated with increased DM (hazard ratio [HR] 2.6, $p = 0.015$) and BF (HR 1.5, $p = 0.018$). "We did not find a significant association in the PSADT six- to 12-month group," notes Dr. Campbell. "The faster a patient's PSA doubling time, the more likely they are to experience recurrence after SRT."

The team also noted a significant association between an initial postoperative PSA of ≥ 0.5 ng/mL and risk of BF, when compared with a postoperative PSA of < 0.2 ng/mL (HR 1.4, $p = 0.046$).

"Our results confirm our previous finding that early SRT at lower pre-SRT levels improves rates of recurrence," says Dr. Campbell. "Incorporating PSA kinetics allows us a more precise look at potential outcomes."

Calculating patients' results

Patients with prostate cancer are a heterogeneous group, making mortality and outcomes prediction complex for physicians to calculate and share.

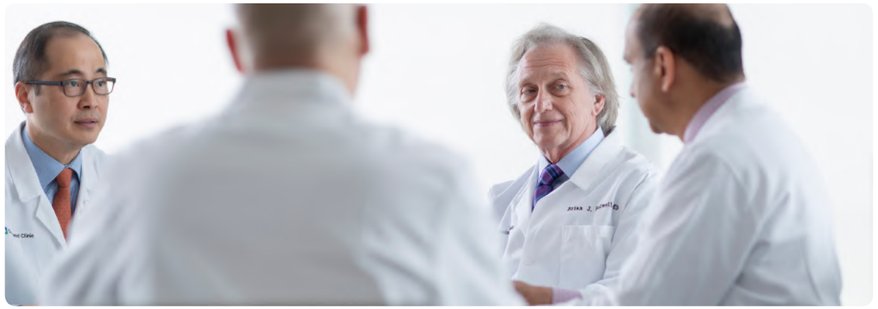
> "Incorporating PSA kinetics allows us a more precise look at potential outcomes."
>
> — SHAUNA CAMPBELL, DO

"Our nomogram update adds an important tool in the physician-patient discussion, because it takes 12 individual characteristics into consideration, so it's quite personalized," says Dr. Campbell. "Patients with this disease are very interested in long-term outcome estimates, and we want to offer them the best answers possible with these 10- and 15-year predictions."

A preview of the nomogram was presented at ASTRO, and the team is developing an online calculator built from the nomogram that will be available to providers and patients within the next year.

CHAIRMAN'S Q&A:

Brian J. Bolwell, MD, FACP, Talks About Physician Leadership



LEFT: John Suh, MD, Brian Bolwell, MD and Jame Abraham, MD, of Cleveland Clinic Cancer Center.

Q: As someone who regularly reads leadership books, you've noted that few, if any, address leadership in a healthcare setting. Why is that?

Dr. Bolwell: Anyone who has tried to figure out medicine realizes how complex it is, organizationally. It is practiced in different environments. Big academic medical centers are usually the focus, but most medicine is practiced in the community. Then there is the complexity of the healthcare ecosystem, in which the pharmaceutical industry, the insurance industry and government regulation all play huge roles. It is very complicated. Having said that, I think leadership, especially physician leadership, has long been ignored in medicine. And I think there is a new appetite to try to learn about it, because both community and academic organizations realize if they want to get things done, they need physician leaders.

Q: Does medicine produce well-qualified leaders?

Dr. Bolwell: In academic medicine, we teach individuals to excel at skills that do not make a good leader. You are rewarded for self-promotion. You are rewarded for individual achievement — for getting grants, for being the first author of publications in high-impact journals. You are rewarded for being invited to speak in front of thousands of people at national meetings. It is a very egocentric system. Leadership has nothing to do with this. Leadership is about serving the team. I believe your job as a leader is to recruit good people, to support them, to create a psychologically safe atmosphere for people to participate and to remove obstacles, which are frequently political. And when success is achieved, to let the team celebrate it. So to think that an individual who has a well-funded lab and is on all sorts of podiums automatically has the skill set to lead teams and be a serving leader is illogical. And yet, that is how leaders are chosen.

Q: How do you change that?

Dr. Bolwell: By changing the recruitment process for physician leaders. I recruit for emotional intelligence. I recruit for grit, which is a combination of passion and perseverance. I do not care all that much about whether you went to an Ivy League school. Having a huge academic pedigree is nice, but it certainly is not the No. 1 prerequisite for getting a job here.

Q: How do you identify those qualities in a candidate?

Dr. Bolwell: I ask questions. I try to measure how people react in real-world situations. You put candidates in a social situation. Things like recruiting dinners are time-consuming, but if you want to adequately evaluate someone, they are a very good idea. The other thing is, in my role as Director of Physician Leadership, I am revamping the search committee process to make it more uniform, by identifying the traits we are looking for and developing structured interview questions.

Q: Are search committees necessary?

Dr. Bolwell: Yes. They know the salient issues in fairly short order, which is useful. The key is to educate people within the search process. So we have brought in the Office of Physician Recruitment to sit on search committees, to bring a certain level of expertise.

Q: Does one have to have been a leader to be a good leader? Do you always look for leadership experience?

Dr. Bolwell: Not necessarily. I think you want someone who has the skill set and is willing to learn, willing to be humble, willing to continually study, willing to receive constructive criticism, willing to want to get better. In academic medicine, many leadership jobs are simply about securing big grants and that is how you are judged, as opposed to managing people. Physicians are very difficult to manage. They are an independent lot. They tend to question everything — we're trained to do that.

Q: In addition to administrative responsibilities, many of Cleveland Clinic's physician leaders also care for patients. And you supervise other physicians who treat patients. How do you manage that dynamic, especially in the cancer setting, where illnesses often are life-threatening?

Dr. Bolwell: It can be emotionally intense. Some literature suggests that oncologists have the highest suicide rate of any subspecialty. You can probably understand why. We have to be aware of that — to be able to acknowledge the fact that this is a stressful thing to do, and that sometimes that stress carries over into what is going on in an individual's home and family life. Part of my job is to make sure we have enough resources and support to help everyone get through their day to the best of their ability.

Q: Once you've found a good physician leader, how do you keep them?

Dr. Bolwell: If I am adhering to the principles I believe in, like being honest and transparent and creating a psychologically safe environment and being willing to accept feedback, hopefully that is an environment that people like to work in. One my favorite lines from one of the leadership books I have read is that great teams are a magnet for great talent. People are reluctant to leave a great team. Sometimes it happens, but it does not happen very frequently.

Q: What do you like about being a leader?

Dr. Bolwell: Leadership is about forming relationships and developing teams. I really like the people here. We have accomplished a lot of great things together in the past decade, and that has been very rewarding. Being able to do some things that are starting to take hold on a national level, like significantly reducing cancer patients' waiting times from diagnosis to treatment, is also rewarding. The positives are real, but the job is not for everyone.

Q: What have you learned from being a leader?

Dr. Bolwell: I have a lot of resources at my disposal. I have used executive coaching a couple of times, which has been really, really good. I am actually learning how to be an executive coach myself. Deeply exploring psychology and motivation — my own as well as others' — has been a useful tool to try to manage the challenges and the solitary nature of the job. The hardest thing is to have the courage to speak up when the environment is not psychologically safe to do so. It is the right thing to do, but it is hard.

Q: How do you become a better leader?

Dr. Bolwell: You cannot just read about it. You cannot just talk about it. You actually have to change what you do. Your behaviors have to change. That is very hard for most people, but you can get better. You can transform, you can connect, you can elevate. It is very difficult, but if you do it well, you get a lot of nice rewards.

Dr. Bolwell is Chairman of Taussig Cancer Institute, Cleveland Clinic Cancer Center, Professor of Medicine at Cleveland Clinic Lerner College of Medicine, and Director of Physician Leadership and Development for Cleveland Clinic. He speaks and writes often about healthcare leadership topics, including in his blog, "Straight Talk," for Oncology Times.

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JAME ABRAHAM, MD, FACP,

Named Chair of Hematology and Medical Oncology

Jame Abraham, MD, FACP, is Cleveland Clinic Taussig Cancer Institute's new Chair of the Department of Hematology and Medical Oncology.

Dr. Abraham will recruit and develop staff and guide the department's focus on patient access and multidisciplinary care.

Most recently, Dr. Abraham was Director of the Breast Oncology Program and Co-Director of the Cleveland Clinic Comprehensive Breast Cancer Program.

He served as Chief of Hematology/Oncology, Professor of Medicine and Bonnie Wells Wilson Distinguished Professor of Breast Cancer Research at West Virginia University before joining Cleveland Clinic in 2013.

Dr. Abraham is national principal investigator for multiple breast cancer clinical trials and has published and presented more than 200 papers. He is Founding Editor of *The Bethesda Handbook of Clinical Oncology* and is involved in national breast cancer committee and leadership activities.

VELOSANO: A CATALYST FOR HIGH-IMPACT CANCER RESEARCH

Treatment advances have produced significant declines in cancer mortality among children and adolescents in the past two decades, but subsets of pediatric patients with solid tumors fail to fully respond and instead relapse.

A novel research project that aims to improve understanding of solid tumor development, progression and therapeutic resistance is underway at Cleveland Clinic Cancer Center. It would not have been possible without funds raised by VeloSano, the annual cycling event that benefits Cleveland Clinic cancer research.

The $213,000 project establishes a biorepository for sequential blood and tumor samples collected from pediatric and young adult patients with solid tumors and supports advanced testing to analyze the tumor microenvironment and its interaction with patients' immune systems. It was one of 12 recipients of VeloSano Impact Awards in 2018. Impact Awards address strategic cancer research priorities at Cleveland Clinic.

By collecting multiple blood samples from diagnosis through treatment, researchers can look for changes in immunobiology that may be associated with therapeutic response or resistance, says Principal Investigator Rabi Hanna, MD, Chair of Cleveland Clinic Children's Department of Pediatric Hematology and Blood and Marrow Transplantation. A particular focus is myeloid-derived suppressor cells, which can suppress T-cell function and prevent effective anti-tumor response.

"We know that immunotherapy, including checkpoint inhibitors, has not been successful in pediatric solid tumors, and part of that may be due to the tumor microenvironment," Dr. Hanna says. "This project could help us understand the possible reasons for relapse, and how we might use immunotherapy in a different way that could make it more effective, with fewer side effects."

The more than $21 million raised by VeloSano in its six-year history — including $4.7 million from the 2019 event — has supported 139 research projects to date. One hundred percent of the dollars raised are applied directly to cancer research. In addition to the Impact Awards category, VeloSano Pilot Awards provide initial funding for projects with a high likelihood of eventually qualifying for external grants.

"As a researcher, VeloSano gives you the freedom to think outside the box and explore concepts that could be high risk, but high reward, too," says Dr. Hanna, who participates on a Cleveland Clinic Children's cycling team of caregivers and former patients that has raised $40,000. "The data we gather from our project could be the seed for a bigger grant in the future. It's research that will hopefully change clinical practice. VeloSano makes those dreams possible."

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ABOUT CLEVELAND CLINIC

Cleveland Clinic is a nonprofit, multispecialty academic medical center integrating clinical and hospital care with research and education for better patient outcomes and experience. More than 3,900 staff physicians and researchers in 180 medical specialties provide services through 26 clinical and special expertise institutes. Cleveland Clinic comprises a main campus, 11 regional hospitals and more than 150 outpatient locations, with 19 family health centers and three health and wellness centers in northern Ohio, as well as medical facilities in Florida, Nevada, Toronto and Abu Dhabi. Cleveland Clinic is currently ranked as one of the nation's top hospitals by U.S. News & World Report.

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