

Multidisciplinary Globe-Sparing Treatment for Lacrimal Gland Carcinoma Preserves Vision and Minimizes Morbidity

By Jill Delsigne

Until recently, the treatment of lacrimal gland carcinoma almost always required removal of the eye. But for some patients with these tumors, globe-sparing surgery followed by radiation therapy can preserve vision and decrease ocular morbidity and facial disfigurement.

Carcinomas of the lacrimal gland, although rare, are associated with a high risk of recurrence, perineural invasion, and distant metastasis. About half of patients eventually die of their disease despite treatment.

Treatment for lacrimal gland carcinoma historically entailed orbital exenteration (removal of the eye and all orbital contents), usually followed by high-dose radiation therapy to address perineural invasion or close surgical margins.



Scott Durham (right), who underwent globe-sparing surgery and radiation therapy for lacrimal gland carcinoma in 2013, attends a follow-up appointment with **Dr. Bitá Esmaeli**. Mr. Durham remains cancer-free and has good visual acuity.

Surgeons were reluctant to preserve the eye because of concerns that the eye would be severely damaged by the radiation therapy.

In recent years, however, the routine use of orbital exenteration for lacrimal gland carcinoma has been called into question by efforts led by Bitá Esmaeli, M.D., a professor of ophthalmology and the director of orbital oncology and ophthalmic plastic surgery at The University of Texas MD

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DAILY NEWS

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Globe-Sparing Treatment

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Anderson Cancer Center. Retrospective reports from MD Anderson and other centers found poor survival outcomes despite local control of the tumors in patients who underwent orbital exenteration. “Orbital exenteration has not shown any survival benefit,” Dr. Esmaeli said.

The globe-sparing approach

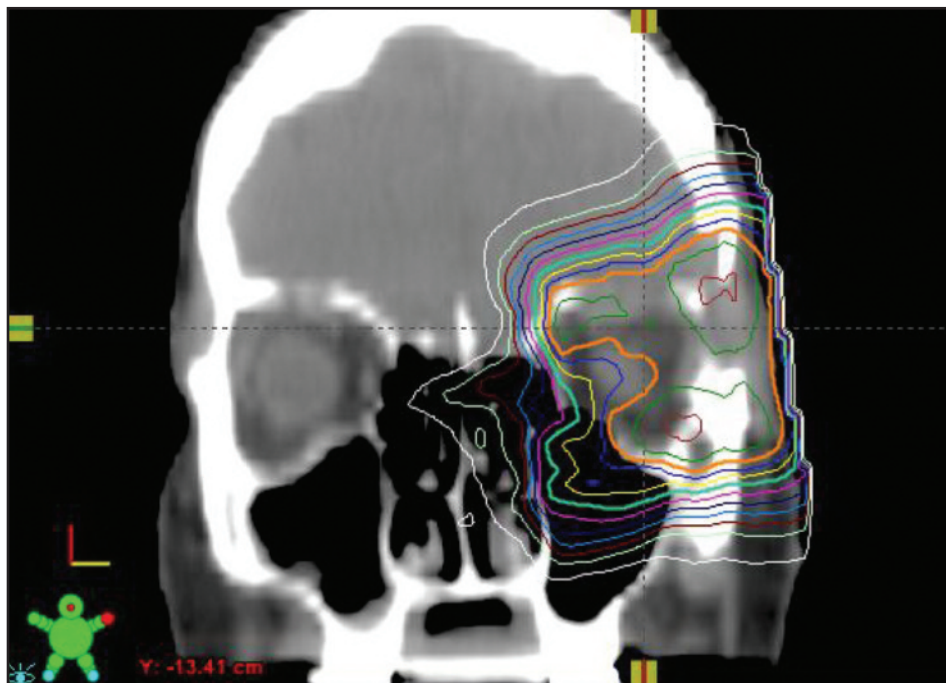
MD Anderson physicians led by Dr. Esmaeli and Steven Frank, M.D., an associate professor in the Department of Radiation Oncology and the medical director of the Proton Therapy Center, use a multidisciplinary globe-sparing approach to manage lacrimal gland carcinoma in selected patients while striving to preserve vision and cosmesis.

This approach involves globe-sparing surgery followed by high-dose adjuvant radiation therapy. Chemotherapy may be given along with radiation to patients with positive surgical margins or recurrent disease.

Dr. Frank said, “With exenteration, a functioning organ is removed because of an adjacent tumor. Our goal is to preserve the eye and its function through surgery and radiation therapy.”

The extent of surgery depends upon the tumor’s location in the lacrimal gland, which comprises the orbital lobe and the palpebral lobe, and the involvement of the orbital soft tissue. For most patients, a significant amount of the orbital lobe must be removed; some patients must also undergo resection of the palpebral part of the gland, which is closest to the eye. Dr. Esmaeli said, “To achieve the goal of resecting the lacrimal gland cancer but preserving the eye and functionally important tissues in the orbit as much as possible, the orbital surgeon must have experience with meticulous oncologic resection.”

The globe-sparing approach requires close collaboration among the orbital surgeon, medical oncologist, and radiation oncologist. This collaboration is especially important in radiation treatment planning, as the treatment field must cover the postoperative surgical bed and often must extend to the base of the skull, toward the brain stem, to



In a proton therapy treatment plan for a patient with lacrimal gland carcinoma, isodose curves show the radiation dose to the tumor bed (6,600 cGy, red lines) and decreasing doses to surrounding areas (lowest dose: 1,500 cGy, white line).

prevent perineural invasion and disease recurrence.

Innovations in radiation therapy

The first MD Anderson patient to receive globe-sparing surgery for lacrimal gland carcinoma was treated in 2007. The surgery was followed by intensity-modulated radiation therapy. Unfortunately, this patient, who received a radiation dose greater than 45 Gy to

the cornea, developed severe corneal toxic effects that eventually necessitated enucleation. The patient has, however, remained disease free. Dr. Frank and his team of radiation oncologists were able to modify the isodose curves in subsequent patients to significantly reduce the risk of corneal toxicities.

The majority of patients who undergo globe-sparing surgery for lacrimal gland carcinoma are now treated with

Lacrimal Gland Carcinoma

Adenoid cystic carcinoma is the most common type of primary malignant epithelial tumor of the lacrimal gland (60%), followed by carcinoma ex pleomorphic adenoma (20%), de novo adenocarcinoma, and mucoepidermoid carcinoma. Of these tumors, adenoid cystic carcinoma has the most aggressive biology; perineural spread occurs in about 75% of patients. Adenoid cystic carcinoma tends to be diagnosed in younger patients than other subtypes

of lacrimal gland carcinoma: the mean patient ages at diagnosis are 37 years and 56 years, respectively.

Symptoms of lacrimal gland carcinoma include globe displacement, vision problems, a palpable mass on the upper eyelid, and eye or periocular pain. Computed tomography and magnetic resonance imaging are necessary to determine the size and shape of the tumor and to estimate the involvement of surrounding tissue. ■

intensity-modulated proton therapy. According to Dr. Frank, "Proton therapy is very effective because we can shape the radiation dose for the complex anatomy while minimizing the dose to the cornea and other optic structures." Proton therapy also eliminates the exit radiation dose that occurs in photon therapy.

Dr. Frank uses several special proton delivery techniques to minimize the radiation dose to avoid damaging the cornea, optic nerve, optic chiasm, and other critical structures. For example, Dr. Frank uses a combination of active scanning and passive scattering radiation to minimize the radiation dose to the optic nerve. However, the target area still receives an appropriate radiation dose (54–60 Gy) for treating microscopic and gross residual disease.

Dr. Frank also uses a custom-made mold to ensure immobilization for patients during proton therapy. The mold, which includes a head and shoulder structure and a mask with a bite block, prevents movement greater than 1 mm. Patients typically undergo 15-minute proton treatment sessions 5 days a week for 6 weeks.

The use of precisely targeted radiation therapy has helped minimize the toxic effects of radiation. All patients treated with the globe-sparing approach have experienced dry eye syndrome, which was expected since the lacrimal gland was removed and the lacrimal fossa was irradiated. One patient also experienced mild radiation retinopathy, and one patient (described above) experienced severe corneal and conjunctival damage, which required enucleation.

Patient selection

"We are one of the first centers to use this multidisciplinary globe-sparing approach," Dr. Esmaeli said. "We carefully select our patients and have been closely observing our patients treated with this approach to learn about the local control rates and also the ocular toxicity associated with this multimodality treatment strategy."

The decision to undergo globe-sparing treatment for lacrimal gland carcinoma is made by the orbital surgeon, the radiation oncologist, the medical oncologist, and the patient. Dr. Esmaeli

MD Anderson's Orbital Oncology and Ophthalmic Plastic Surgery Program

The orbital oncology and ophthalmic plastic surgery program in the Department of Plastic Surgery at MD Anderson specializes in surgical treatment of tumors of the orbit, eyelid, conjunctiva, eye, and ocular adnexal structures as well as reconstructive surgery in the periocular region. It is the only dedicated orbital surgery and ophthalmic plastic surgery program based at a comprehensive cancer center in the United States. The primary goals of this program are eliminating ocular and orbital cancers while preserving the eye and vision and restoring function and cosmesis in the periocular region.

The orbital surgeons work closely with surgeons from other disciplines such as plastic surgery, head and neck surgery, skull base surgery, and neurosurgery and with radiation oncologists and medical oncologists to develop multidisciplinary treatments for orbital and ocular cancers.

The orbital oncology and ophthalmic plastic surgery program is led by Dr. Bitu Esmaeli, who pioneered the sentinel lymph node biopsy technique for eyelid and ocu-

lar adnexal cancers. Dr. Esmaeli is also the principal investigator for a tissue banking study for uveal melanoma and the co-chair of The Cancer Genome Atlas working group for uveal melanoma.

The orbital oncology and ophthalmic plastic surgery program is currently conducting several clinical trials. Two of these trials aim to detect low-volume metastatic disease through sentinel lymph node biopsy: GSP00-106 for patients with conjunctival and eyelid melanoma and 2008-0266 for patients with sebaceous gland carcinoma of the eyelid. A trial of in vivo confocal microscopy of pigmented conjunctival lesions (2010-0330) is comparing imaging studies between participants with conjunctival melanoma and those with healthy eyes for differences that might lead to earlier diagnosis of these lesions.

For more information about MD Anderson's orbital oncology and ophthalmic plastic surgery program, visit www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/plastic-surgery/orbital-oncology. ■

stressed the importance of counseling patients preoperatively: "Patients should understand the inherently higher risk of local-regional recurrence with globe-sparing surgery and the ocular side effects of radiation therapy. Having said that, with a median follow-up time of over 2 years, none of our first 11 lacrimal gland carcinoma patients treated with a globe-sparing approach has experienced a local or regional recurrence."

Some patients are not good candidates for globe-sparing surgery and are still best treated by exenteration. Indications for exenteration include large tumor size, extensive infiltration of other critical orbital structures, recurrence after previous globe-sparing treatment, high histologic grade, and

patient preference for a more radical surgery to potentially lower the risk of local recurrence.

Expanding the use of globe-sparing treatment

Drs. Esmaeli and Frank said that they also use the globe-sparing approach for other orbital cancers. Dr. Esmaeli said, "We are pushing the frontiers in surgical resection and radiation treatment of orbital cancers with the goal of preserving visual function and cosmesis whenever possible for all cancers that occur in the orbit and periorbital region." ■

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Novel Trial Design Streamlines Development of Breast Cancer Therapies

By Joe Munch

Developing a cancer-fighting drug can take around a billion dollars and a dozen or more years. Even then, about 40% of investigational cancer drugs fail in clinical trials. To identify effective cancer therapies more quickly and efficiently, researchers have turned to an innovative clinical trial model in which multiple treatments are investigated simultaneously and the study design is adapted as patient data accrue.

This model was used to design the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2 (I-SPY 2 TRIAL), which is under way at The University of Texas MD Anderson Cancer Center and other centers. I-SPY 2, which is open to patients who have localized breast cancer, may be a harbinger of a new paradigm in cancer drug development.

“Whenever we have a new agent, we always like to find the patient populations in which it will work best,” said Stacy Moulder, M.D., an associate professor in the Department of Breast Medical Oncology and the trial’s principal investigator at MD Anderson. “This trial is designed to help us understand where new drugs are best positioned to treat localized breast cancer. This helps patients in the long run.”

A departure from convention

At first blush, I-SPY 2 does not seem all that different from a conventional clinical trial: The phase II study enrolls women with newly diagnosed stage I–III invasive breast cancer whose tumor is at least 2.5 cm in diameter; its endpoint is pathological complete response (pCR; defined as no residual invasive cancer in the breast or lymph nodes at the time of definitive surgical

resection). Patients are randomly assigned to receive standard therapy—12 weekly cycles of paclitaxel (patients with human epidermal growth factor receptor 2 [HER2]–positive tumors also receive trastuzumab)—with or without an investigational new drug. All patients then receive four 2- or 3-week cycles of an anthracycline (e.g., doxorubicin) and cyclophosphamide followed by surgery to resect the tumor.

But closer examination reveals that the trial has several unique features that set it apart from conventional models. Chief among these features is the use of tissue and imaging biomarkers first to determine study eligibility and later to identify which patient subsets benefit most from a particular therapy.

Biomarker data are gathered throughout the study. Prior to treatment, patients undergo magnetic resonance imaging (MRI), core needle tissue biopsy, and blood tests. Specimens are assessed for common breast cancer biomarkers, including the estrogen, progesterone, and HER2 receptors. A genomic assay that evaluates the expression levels of 70 breast cancer–related genes is performed to determine patients’ recurrence risk. MRI and blood draws to monitor tumors’ therapy response are repeated after the third paclitaxel cycle and again at the conclusions

of the paclitaxel and the anthracycline-and-cyclophosphamide phases. Patients also undergo a second core biopsy after the third paclitaxel cycle.

Donald Berry, Ph.D., a professor in the Department of Biostatistics at MD Anderson, collaborated with Laura Esserman, M.D., a professor of surgery and the director of the Carol Franc Buck Breast Care Center at the University of California–San Francisco’s Helen Diller Family Comprehensive Cancer Center, to design I-SPY 2. Dr. Berry is the multi-institutional trial’s co-principal investigator.

“In I-SPY 2, because we don’t want to wait to learn how well the individual patients are doing, we do these tests over time to understand and model the relationship between what we can see in the tumor and the eventual pCR,” Dr. Berry said. “This is something that is surprisingly revolutionary—to actually look at the whole patient and how the patient is doing over time rather than just looking back retrospectively.”

A neoadjuvant therapy approach

Although not an innovation of I-SPY 2 per se, the use of a neoadjuvant treatment approach is a key element of the trial’s design. Clinical trials of neoadjuvant treatments have endpoints that can be assessed more quickly than those of adjuvant therapy trials.

In many cases, breast cancer patients first undergo surgery to remove the tumor and then receive adjuvant systemic therapy to eliminate any residual disease. Adjuvant therapies for breast cancer have greatly improved over time, leading to longer survival durations; indeed, the 34% drop in breast cancer–related mortality in the United States since 1990 has largely been attributed to these agents’ increasing effectiveness. However, the success of such agents given as standard therapy has made it more difficult to investigate new drugs in the adjuvant therapy setting.

“This drop in breast cancer mortality is a wonderful thing, but it does imply

statistically that it is harder to run a trial; larger sample sizes are required because there aren't as many events as there once were," Dr. Berry said. "Testing a drug in the adjuvant setting now requires 5,000–10,000 patients, and it just isn't sustainable."

In contrast, therapy given before the tumor is removed provides researchers the opportunity to rapidly assess the tumor's response, enabling them to more quickly discern whether the treatment is effective.

"From a drug development standpoint, the neoadjuvant approach is very powerful because you can have an endpoint—pCR in this case—that has been associated with long-term survival outcomes in patients with breast cancer," Dr. Moulder said. "It can take years to determine if a drug had any benefit when it's given in the adjuvant setting, but when you measure pCR in the neoadjuvant setting, you can get that data in 6 months and know what impact your drug is having."

Investigating multiple drugs

The I-SPY 2 model improves upon conventional clinical trials in part because it evaluates multiple investigational drugs from different manufacturers simultaneously. This "platform" design, which Dr. Berry likens to trucks from various companies backing up to a warehouse platform and unloading their payloads for evaluation, enables researchers to add drugs to the trial without having to amend or rewrite the study protocol. That's not to say that all comers are welcome, however. Agents are heavily vetted by the trial's Independent Agent Selection Committee before they are added to the study. To be added, agents must have a fairly robust bioresponse or benefit profile in the metastatic disease setting and have sufficient toxicity data to allow investigators to anticipate and address potential side effects, Dr. Moulder said.

I-SPY 2's platform design also enables researchers to compare multiple therapy regimens to a common control, which greatly reduces the number of patients required to test drugs compared with conventional clinical trials. Currently, I-SPY 2 has six arms: five



Dr. Stacy Moulder



Dr. Donald Berry

experimental and one control. If these five experimental regimens were to be evaluated in separate two-arm randomized trials, 10 arms would be required.

From a patient standpoint, I-SPY 2's platform design, with its common control arm and high bar for including experimental agents, offers another important benefit: a better chance of being assigned to a potentially effective experimental therapy. In a two-arm randomized study, the likelihood of a patient being assigned to the experimental therapy is 50%; in I-SPY 2, that likelihood is 80%.

"Because there are multiple agents within the study, patients have a good opportunity of getting an investigational agent that, by virtue of being in the study, appears promising," Dr. Moulder said.

Adaptation

"The biggest innovation of I-SPY 2 is that we actually look at the data as they accrue and tailor the study design to what we're seeing," Dr. Berry said. He explained that all possible adaptations are programmed in advance, and adjustments to the ongoing trial are carried out by a computer algorithm. Dr. Berry monitors these adjustments to ensure that the algorithm is functioning as expected.

Unlike conventional clinical trials, I-SPY 2 uses adaptive randomization to assign patients to study arms. An automated algorithm performs the randomization. As the study progresses, newly acquired patient data—biomarker information and pCR rates—are fed into the algorithm, and the probability of a new patient's being assigned to a particular experimental therapy changes over time depending on the past performance of that therapy in other patients with the same disease subtype. Thus, Dr. Berry

said, "Patients who belong to a subset in which a drug isn't doing very well are unlikely to get the drug. Adaptive randomization gives us the ability to focus in on which subsets of patients are benefiting from a therapy. You can't do that using a standard approach."

As an example, Dr. Berry points to neratinib, one of the drugs initially included in the study. The HER2-family tyrosine kinase inhibitor was eliciting strong antitumor responses in some patient subsets but not others. Seeing this, the study's Data Safety and Monitoring Board suggested amending the study so that patients in the subsets in which neratinib was showing little benefit would no longer be considered for the drug. Dr. Berry said, "I told them, 'You don't have to do that; the algorithm is already doing it for you. Look at the randomization probability for that patient subset: it's zero.'"

Graduation

An investigational drug regimen "graduates" from I-SPY 2 to the next phase of testing if Bayesian analysis determines that the treatment would likely provide a benefit over standard neoadjuvant therapy in at least one patient subset if given in a 300-patient phase III trial. Once a treatment graduates, accrual in that experimental arm stops, and the drug is moved into a phase III trial.

Two treatments thus far have graduated from I-SPY 2. The first to graduate was the combination of the poly(ADP-ribose) polymerase inhibitor veliparib plus carboplatin. The second was neratinib. Given alongside standard neoadjuvant therapy, the veliparib-carboplatin combination and neratinib showed promise in patients with triple-negative breast cancer and in patients with HER2-positive, hormone receptor-negative disease, respectively. Just as important, the regimens were identified as having very little potential in patients with other breast cancer subtypes, which effectively eliminated the two therapies from further investigation in those groups.

"If a drug doesn't graduate, or if it doesn't appear to benefit certain patient subsets, those are important findings, too," Dr. Moulder said. "That means we

Novel Trial Design

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don't expose a large number of women to a drug that is not likely to be of benefit."

A trial model for the 21st century

Studies using adaptive randomization algorithms to direct investigational new drugs to the patients most likely to benefit from them are under way in other cancers, including melanoma and glioblastoma, as well as in other diseases. As with I-SPY 2, the overall aim of these trials is to use fewer resources to bring effective therapies to patients sooner. The key to doing so, Dr. Berry said, is identifying the ineffective therapies early on.

"We have to eliminate ineffective drugs before they get to phase III trials," Dr. Berry said. "In Alzheimer disease, for example, the last 20 phase III trials have failed. There's something wrong with this picture."

Dr. Moulder agreed. "To have all the resources and patient numbers go into a study that demonstrates no benefit is really problematic. Conducting really large trials without any selection diminishes the pool of eligible patients for clinical trials where there actually is some benefit."

Acknowledging the need to streamline the drug-development process, members of Congress have unveiled the 21st Century Cures Initiative. This measure, which proposes enacting legislation that advocates the use of Bayesian statistics and adaptive randomization in clinical trials, indicates a potential sea change in the way therapies for cancer and other diseases are brought from the bench to the bedside.

"I think it's the coming thing," Dr. Berry said. "Everybody sees the benefit of asking multiple questions in the same trial and moving with the flow of the data." ■

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To learn more about the I-SPY 2 TRIAL, visit www.clinicaltrials.org and select study No. 2010-0145.

Targeted Therapy for High-Risk Melanoma May Forestall Recurrence

By Bryan Tutt

Although targeted agents have been approved for the treatment of metastatic melanoma, such agents typically are not used in patients with earlier-stage, resectable disease who have a high risk for recurrence. But a clinical trial of targeted therapy before and after surgery aims to prolong recurrence-free survival for patients with resectable high-risk melanoma.

For patients who have high-risk stage III melanoma—disease that has spread to the lymph nodes—the standard of care is surgery followed by observation or adjuvant treatment with high-dose interferon. While interferon is the standard adjuvant therapy for this group, many physicians believe the drug's side effects outweigh its modest benefit. "Interferon's numerous side effects make this drug difficult to tolerate, and data suggest only a small degree of reduction in the risk of disease recurrence," said Rodabe Amaria, M.D., an assistant professor in the Department of Melanoma Medical Oncology at The University of Texas MD Anderson Cancer Center.

The need for more effective treatments for patients with high-risk stage III disease is critical, according to Jennifer Wargo, M.D., an assistant professor in the Departments of Surgical Oncology and Genomic Medicine.

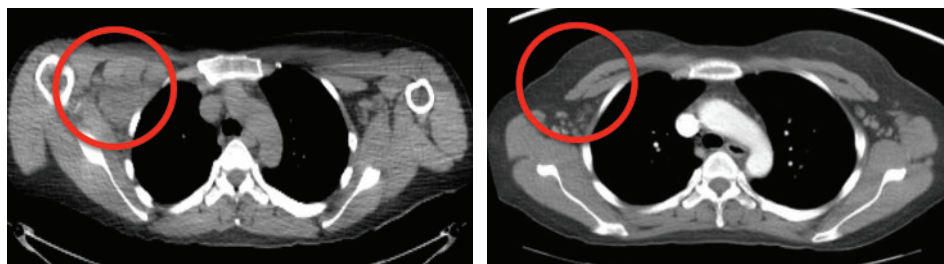
"Up to 70% of patients with high-risk resectable melanoma ultimately die of their disease," she said. Drs. Wargo and Amaria think that patients with high-risk resectable disease may benefit from some of the new targeted drugs used to treat metastatic disease.

BRAF and MEK inhibitors for metastatic melanoma

Among the recent advances in melanoma treatment has been a class of drugs called BRAF inhibitors.

BRAF gene mutations occur in about half of cutaneous melanomas. The mutated BRAF protein activates MEK and other kinases along the MAP signaling pathway, stimulating cancer cell growth and proliferation. Blocking BRAF's activity shuts down the MAP pathway, but only temporarily. "The BRAF inhibitors work well for about 6 months, but then in some patients we see reactivation of

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Computed tomography scans of a 47-year-old patient show melanoma that had spread to the lymph nodes of the right underarm (red circles). The disease was initially considered unresectable (left), but marked tumor reduction after 8 weeks of therapy with dabrafenib and trametinib (right) made possible resection, which revealed no residual viable tumor.



Interpreting Health News

Common mistakes in medical reporting

News reports sometimes give questionable medical advice.

Here are some big mistakes to watch out for in health news and what to pay attention to instead.

DAILY NEWS

Relying on weak evidence

When a news report says, “Studies show . . .,” you should ask, “What kind of studies?” Some types of studies provide evidence strong enough to change medical practices, but others cannot by themselves guide reasonable decisions about your health. Look for the following problems:

Citing observational, not experimental, studies. News stories frequently feature observational studies, in which scientists gather information about various groups of people and look for patterns. Observational studies can show a statistical link between two factors but do not always account for other important factors. For example, a study that shows a relationship between more education and a longer lifespan might not account for the effects of income on both. Results of this kind can signal a need for more research but cannot prove that one thing causes another.

Instead, look for experimental studies, in which scientists recruit participants, give some of them an intervention—anything from medication or surgery to a change in diet—and then see how that intervention affects certain outcomes.

In particular, pay attention to news that cites randomized controlled clinical trials. In these studies, volunteer patients with similar characteristics are randomly divided into a group that receives an experimental treatment and a group that receives the current standard treatment or, if no standard treatment exists, a placebo. The strongest experimental evidence comes from systematic reviews and meta-analyses, which draw conclusions from the combined results of multiple clinical trials.

Citing preclinical, not clinical, studies. New drugs are tested in cells outside the body and then in animals such as mice before they are tested in humans, and these studies are too pre-

liminary to directly affect patients. It’s interesting to hear that cancer cells die when treated with a new drug in a laboratory, but much more research is needed to show that the drug has the same effect inside the human body. Keep in mind that most drugs that seem to work in laboratory or animal studies ultimately don’t work in humans.

Citing anecdotes. The experiences of one patient or one doctor, or the experiences of a handful of patients and a handful of doctors, do not add up to conclusive evidence.

Exaggerating benefits and minimizing harms

A health news report needs to get specific when reporting how much an intervention affects an outcome. If you hear that yoga causes weight loss, ask how much weight and how much yoga; the effect could be negligible. Relative measures like “4 times more” or “3 times less” often conceal the true size of an effect. If you hear that coffee “halves” the risk of a particular type of cancer, find out what that risk is to begin with. If the original risk is very small—say, a risk of 0.5% over a lifetime—then halving that risk wouldn’t make much of a difference.

Also, the intervention’s possible side effects, along with their likelihood and severity, should always be mentioned; but some news reports skip this discussion. If the side effects of an intervention are not yet known, then that uncertainty should be frankly acknowledged.

Ignoring the options you already have

A new drug or procedure isn’t always better than the treatments that are al-

ready used for the same purpose. A report introducing an intervention should compare that intervention with current standard approaches. The option of simply not receiving the new intervention should be considered, too; for example, a condition that could be treated with a new surgical procedure could instead be managed through watchful waiting.

Ignoring availability or cost

Many reports about new interventions fail to talk about access. New treatments and tests that have not completed the clinical trials required for government approval can be given only to patients who are selected to participate in those trials. Such trials may take months or years to complete and may take place at only a few hospitals. Also, a complex procedure can take time to become widely used and may be available only through specially trained doctors.

In addition, interventions that have reached the public market may be widely available but not affordable. Insurance policies may not cover a new treatment or test, or the copay may be prohibitively high.

Reliable sources of health information

The common mistakes discussed in this article and the characteristics of good health news stories are described at www.healthnewsreview.org. For clearly written summaries of clinical effectiveness research, visit PubMed Health at www.ncbi.nlm.nih.gov/pubmedhealth. Your doctor is also a reliable source of health information; talk to him or her before making health decisions based on news reports. ■

— S. Bronson

FOR MORE INFORMATION

- Ask your physician
- Call askMDAnderson at 877-632-6789

High-Risk Melanoma

[Continued from page 6]

the MAP kinase pathway,” Dr. Wargo said. “So we add a MEK inhibitor to block the pathway at a different point, and that extends median progression-free survival to about 10 months in patients with metastatic melanoma.”

The oral BRAF inhibitor dabrafenib and the oral MEK inhibitor trametinib were approved separately by the U.S. Food and Drug Administration in 2013 for the treatment of patients with BRAF-mutant metastatic melanoma. The combination of the two drugs was approved in 2014 for the same indication.

Clinical trial for high-risk resectable melanoma

“Because of the success we’ve seen with dabrafenib and trametinib in patients whose melanoma has spread throughout their bodies, we’ve opened a clinical trial to extend this therapy to patients with earlier-stage disease,” said Dr. Wargo, the principal investigator of a clinical trial in which patients with high-risk melanoma receive dabrafenib and trametinib before and after cancer surgery.

The study is currently enrolling patients with stage IIIB, stage IIIC, or resectable oligometastatic (stage IV, spread to three or fewer areas) melanoma with BRAF mutations. Patients are randomly assigned to receive surgery without adjuvant therapy (the current standard of care) or surgery preceded by 8 weeks of dabrafenib and trametinib and followed by 44 weeks of the drug combination.

Thus far, the drug combination has

been well tolerated by patients in the trial, although the side effects can include fever and chills, fatigue, and joint pain. Although results of the trial are not yet available, Dr. Wargo is optimistic that the drugs will decrease patients’ recurrence risk. “I’ve seen patients who were treated with this drug combination before surgery whose tumors went away entirely—a pathological complete response,” she said.

Drs. Amaria and Wargo are hopeful that neoadjuvant therapy will prove as effective against melanoma as it has against other cancers. In addition to killing micrometastases that could lead to recurrence, preoperative therapy with dabrafenib and trametinib may make local and regional disease more amenable to surgery. Neoadjuvant therapy might downstage tumors, making less extensive surgery possible in some patients or enabling negative surgical margins to be achieved.

Dr. Amaria said, “We as a community of oncologists need to think differently about how we treat patients with high-risk melanoma. If this regimen improves survival outcomes as we predict it will, I think this trial could lead to a paradigm shift in the treatment of this patient population.” ■

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To learn more about the clinical trial of BRAF and MEK inhibitors for the treatment of high-risk melanoma, visit www.clinicaltrials.org and select study No. 2014-0409 or contact Dr. Jennifer Wargo at jwargo@mdanderson.org.

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