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Increasing Focus on the Difficult Issue of Discussing the Cost of Care with Patients

BY ERIC T. ROSENTHAL

ASCO is readying a "Guidance Statement" on the cost of cancer care, expected to be published in July in *JCO*. In addition, one of the seven highlighted studies the Society selected for a teleconference two weeks before the Annual Meeting showed that a "significant minority" of patients in clinical trials feel anxious or adopt coping strategies to be able to pay for supportive medications. The same study also documented that cost is rarely discussed among patients and physicians.

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[ALSO]

PERIODICALS

Early Vocal Fold Cancer Presents Delicate Choices

BY THOMAS R. COLLINS

The choice with which laryngologists are faced when it comes to early vocal-fold cancer is a delicate one: How invasive does the treatment need to be at this stage?

A panel of distinguished physicians talked about this fine balance that they must try to strike as they discussed three cases presented by Jesus Medina, MD, Chair of the Department of Otorhinolaryngology at the University of Oklahoma Health Sciences Center in Oklahoma City. The experts sometimes opted for an attempt at an endoscopic procedure and at other times suggested an open procedure, and debated the use of radiation therapy.

At all times, though, they cautioned that all angles should be kept in mind and that, when a treatment can go one way or the other, a fully informed patient will be the best-treated patient.

First Case Study: Persistent Hoarseness

The case that prompted the most discussion was that of a 52-year-old man who arrived at the clinic after having hoarseness for six months. He reported minimal throat discomfort and did not report any ear pain or painful swallowing. At one time, he had smoked 30 pack-years, but had quit smoking when he was 35. He reported no other medical problems.

An image showed that the lesion involved the anterior two-thirds of the left vocal cord but the anterior commissure was not involved.

Dr. Medina first posed a question to William M. Mendenhall, MD, Professor of Radiation Oncology at the University of Florida College of Medicine in Gainesville, about the extent of the radiation portals:

"Radiation portals are usually five by five centimeters in a case like this. Why do we have to cover such a wide field with all the advances in localizing radiation to very small tumors? Why can we not make that field smaller so that we don't have to deal with the cumbersome edema that sometimes develops with radiating a lesion like that?"

The problem, Dr. Mendenhall said, is that the target moves—"The problem is organ motion. You set the patient up, he swallows, and the tumor can slide out of the field or move toward the edge of the field. And normally we set it up by the surface anatomy."

He said, though, that a five-by-five field size is "pretty tight" and that with a T1a lesion, edema wouldn't be too much of a complication.

At this point, Dr. Mendenhall said, he would present the patient with options. "Someone like this would be offered transoral laser resection or radiation therapy and given the choice."

This patient was treated with radiation therapy at 63 cGy in 28 fractions. Then his voice returned to normal. He seemed to have responded well to the therapy.

But 14 months later, he was back, reporting hoarseness again, as well as left ear pain and mild pain when swallowing. This time, the exam revealed a more invasive lesion covering two-thirds of the left cord and thicker in the anterior portion of the cord. There didn't appear to be any cervical adenopathy and the motility of the cords was preserved.

"This is not your run-of-the-mill, pushing-border type of squamous cell carcinoma," as Dr. Medina put it. "It's rather infiltrating."

What Is the Next Step?

Henry Hoffman, MD, Professor of Otolaryngology–Head and Neck Surgery at the University of Iowa, said he would try to get more information: "I'd probably get a CT on this patient. I think it might be a little more extensive than you can see, especially in the face of failure of radiotherapy.

"This is one that, assuming that it shows it to be confined in a way that's not eroding into the cartilage, doing an endoscopic resection" would be best.

He said the pain in the ear and in swallowing was particularly concerning and there was worry about the anterior commissure.

Dr. Medina said, though, that a CT scan "didn't reveal anything unusual."

Dr. Hoffman said his approach is to "emphasize exposure" of the lesion to get a better read on it then use an endoscopic procedure.

"I also counsel the patient that there's probably going to be more than one surgery in store for them because if we do expose the cartilage, which we may need to do to get down to the perichondrium, there are going to be some healing problems after our endoscopic resection.

"The counseling session is a bit prolonged, but I think it sets you up for the appropriate treatment under one anesthetic."

Dr. Medina asked about the difficulty of achieving negative margins with the endoscopic approach.

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→MOLECULAR PROFILING

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much experience with the PFS ratio as a clinical endpoint—that is, with patients as their own controls—so there could be an ascertainment bias if PFS ratios are influenced by the frequency of evaluation.

"But it was encouraging to see that those who had a PFS ratio of 1.3 or greater had better survival than the total population," he said.

Other limitations were the different histological types of tumors entered on the trial; the fact that the trial was nonrandomized; and high patient attrition, dropping from 106 to 66.

But of the 40 patients lost, 30 (75%) were due to worsening condition, he said.

Future trials will be more disease specific, Dr. Von Hoff said, and new methodologies will be incorporated, such as K-RAS sequencing, comparative genomic hybridization, and NextGen sequencing.

Discussant

"These are obviously preliminary results, but this is a very strong step in the right direction," said the Discussant for the study, Ronald A. DePinho, MD, Professor in the Department of Medicine and Genetics at Harvard Medical School and Dana-Farber Cancer Institute. "Many of the abstracts presented in this session speak to the need for doing this kind of work."

Dr. DePinho said there is very good evidence that documentation of a drug target's expression and activity increases the likelihood of efficacy for a drug designed to extinguish that target, such as HER-2/*neu* and trastuzumab in breast cancer.

> Future trials will be more disease specific, and new methodologies will be incorporated, such as K-RAS sequencing, comparative genomic hybridization, and NextGen sequencing.

"And knowledge of a target's signaling circuitry can further inform the deployment of drugs—for example, K-RAS status for EGFRi," he said.

"The challenge we face in implementing personalized cancer medicine is that we currently have an elemental view of the genetic alterations that occur in cancer. And the most important challenge we face is that we have a meager portfolio of cancer drugs, with many pipeline drugs directed against the same targets and pathways. Our ability to actually implement a rational and effective therapeutic program is going to be hampered for some time to come until we increase the repertoire."

A further challenge is that "routine, cost-effective, multi-dimensional high-resolution genomic and proteomic analyses are not yet possible," he said.

"We need inexpensive technologies that catalog all of the key alterations relevant for a particular tumor type, and a dramatic expansion of the cancer drug portfolio, particularly the druggable space" such RNA interference and tissue factors.

Multiple Regimens Suggested by Profiling

The study was conducted at nine centers across the United States. After a tumor biopsy was performed, patients for whom a molecular target was found by IHC, FISH or microarray were treated according to those findings. If not, treatment was that already chosen by the clinician.

Among the 66 patients treated by molecular profiling, 43 were female and 23 male; median age was 60; 9% of patients had one prior treatment, 53% had two to four prior treatments, and 38% had five to 13 prior treatments; 27% had breast cancer, 17% colorectal, 8% ovarian, and 48% other cancers.

Eight different treatment regimens were selected by molecular profiling for the breast cancer patients, including diethylstibesterol, nab-paclitaxel+trastuzumab, nab-paclitaxel+gemcitabine, letrozole+capecitabine, oxaliplatin+fluorouracil+trastuzumab, gemcitabime+pemetrexed, doxorubicin, and exemestane.

Four regimens were selected for colorectal cancer patients, including irinotecan+sorafenib, temozolomide+bevacizumab, sunitinib+mitomycin, and temozolomide+sorafenib.

Lapatinib+tamoxifen was selected for ovarian cancer; cetuximab+irinotecan for non-small-cell lung cancer; cetuximab+irinotecan for cholangiocarcinoma; gemcitabine+etoposide for mesothelioma; sunitinib for eccrine sweat gland cancer; and cetuximab+gemcitabine for gastrointestinal stromal tumors.

He cautioned, though, that some of these treatments represented off-label uses for these standard agents.

Summing up, he said, "With this trial, we are showing the power of personalized medicine using the tools we already have available to us. As these tools become more precise and more effective, the value of personalized medicine will increase."

→VOCAL FOLD

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"Do the characteristics of the tumor, the fact that it's so infiltrating, bother you in terms of your ability to do the laser resection?" he asked. "In these cases, we basically depend on the appearance of the tumor under the microscope as we're cutting it through and then we go into normal tissue. With margins like this, is that a problem, does that limit you?"

"The more aggressive it is," Dr. Hoffman said, "the more uncomfortable I am addressing it endoscopically with a laser and the more likely to convert to an open procedure."

Alternative Approaches

Dennis Kraus, MD, Director of the Speech, Hearing, and Rehabilitation Center at Memorial Sloan-Kettering Cancer Center, proposed a different approach: "This is someone that I think I would be much more inclined to do an open partial laryngectomy on to begin with," he said.

"This man's already failed radiation therapy. Your ability to obtain negative margins is going to be pretty limited. The inner surface of your margin is actually going to be the thyroid lamina, and then looking at the endophytic nature of this tumor, I'm concerned that you could have microscopically positive margins on the inner perichondrium."

Dr. Medina asked how to "put some bulk in the defect" after the surgery.

David Eisele, MD, Professor and Chairman of the Department of Otolaryngology–Head and Neck Surgery at the University of California, San Francisco, said, "The symptoms are disproportionate to the lesion, which I think implies that there's more disease than is clinically apparent here. I would do a vertical hemilaryngectomy on this patient and reconstruct with the strap muscles."

Daniel Brasnu, MD, from the Department of Otorhinolaryngology–Head and Neck Surgery at European Hospital Georges Pompidou in Paris, said his approach depends on the exposure level.

"With this patient, if we can have very good exposure, I would propose endoscopic resection. We still have the opportunity to do an open procedure" if the laser option isn't successful.

Second Case: Endophytic Lesion

In another case, a 67-year-old man reported that he had had hoarseness and throat congestion for five months. He had smoked three packs a day for 46 years but quit three years earlier.

An image showed an endophytic lesion that involved the anterior two-thirds of the vocal cord and extended up to the anterior commissure. There were about 9 to 10 ml of subglottic extension.

Dr. Mendenhall said he wasn't worried much about the anterior commissure. He said that at his institution they had recently reviewed about 500 cases of a similar nature and that "I didn't see any adverse effect of anterior commissure involvement."

Dr. Kraus said he'd opt for radiation therapy but issued a caveat: "I think radiation therapy is the right treatment in this patient. I think the issue, though, is adequate staging.

"A lot of patients that I end up seeing being referred from the outside who've been treated at other institutions who have a recurrence three or four months post-radiation because radiation 'didn't work' with large, bulky subglottic tumors are vivid examples like this patient. The patient wasn't adequately staged and wasn't adequately treated to begin with. I think in tertiary centers where patients are appropriately evaluated, appropriately treated, they do well. But I think a lot of the early failures that we see are a consequence of these patients not being appropriately staged."

Dr. Eisele mentioned several options. "I think the patient is a candidate for an open partial procedure. The major concern I have is the extent of the subglottic extension, but I think he's a candidate for frontolateral hemilaryngectomy or a supracricoid laryngectomy."

But ultimately, he said, "I think from a functional standpoint, he's better served with radiation therapy."

Asked to present options beyond radiation therapy, Dr. Brasnu said that, given that it is "a very limited subglottic extension," he would perform either an open procedure or "maybe, maybe" an endoscopic procedure involving removal of the cricothyroid membrane down to the cricoid arch.

Dr. Medina asked him, "Does that bring about any problems? When you have to resect the cricothyroid membrane, would you get more subcutaneous emphysema in those patients?"

Dr. Brasnu said, "It's not a major problem," and added, "If I would do a resection, I would discuss post-op radiation afterward."

But radiation therapy after the procedure would not be his choice, Dr. Mendenhall said. "I think if you want to do a partial laryngectomy, great, but I would not plan on post-op radiation therapy personally. I'm really worried about causing some major problems with function."

Dr. Hoffman said that a more extensive procedure might help preserve a patient's voice, although that step should be taken only in some cases.

"This type of resection usually leaves an incompetent valve and a significant dysphonia and supraglottic phonation," he said. "We've done a number like this with free-flap reconstruction and restored true glottic phonation.

"It's a long road to go but you do get the best voice as reliably as I've seen with the vertical partial laryngectomies reconstructed in this fashion." But he cautioned that not all patients are candidates for such a procedure and it may be best to leave them with poor voice quality rather than subject them to a large operation.

Third Case: Vocal Cord Dysplasia

In another case, involving a 58-year-old male patient, an image showed severe dysplasia of the left vocal cord, with squamous carcinoma in situ. On the right vocal fold, there was hyperkeratosis with mild dysplasia.

"This appears to be localized," Dr. Eisele said. "I think we need to look at those lesions as basically the same entity, the same biological behavior."

Dr. Hoffman cautioned against a procedure that involved both folds at once. "I would probably hold off on operating on both sides at the same time," he said. "I'd want to leave the right side alone in hopes that you'd remove some irritation by removing the left, and so you'd still maintain the fluidity without inducing a scar by removing the right side of the lesion."

Dr. Medina asked Dr. Mendenhall, "Is there ever a case where you treat with radiation therapy dysplasia and carcinoma in situ in the vocal fold?"

Not very often, Dr. Mendenhall said. He would probably resort to radiation therapy only in the event of a recurrence. "Each time you operate, the voice quality deteriorates. Since 1964, I think we've probably treated less than 30."

The patient was treated with excision using the mucosal flap technique. He recovered well, but was lost to follow-up. Then, a year later, he came back reporting severe hoarseness.

A biopsy showed invasive squamous cell carcinoma on the left cord and severe dysplasia on the right. Vocal cord motility was preserved, and there was no cervical adenopathy, Dr. Medina said. CT scans showed that the lesion was "very superficial, and that there is no invasion of the paraglottic space."

Randal Weber, MD, Chairman of the Department of Head and Neck Surgery at the University of Texas M. D. Anderson Cancer Center said he had asked the patient about these options. "I would present both options to him: laser incision versus standard radiation therapy," he said. "I think it's important that he stop smoking. I would make every effort to get that therapy under way. I'm in favor of radiation."

Dr. Eisele said he would order an MRI for more information. "When you're dealing with recurrence, it's not uncommon for that to be more advanced than the original lesion," he said. "You've achieved negative margins of resection before. Something else is going on. I would just rule out more advanced disease than you can see here endoscopically."

He said, at this point, he would favor radiation therapy, but "I think he's a candidate for a number of different approaches.

"Certainly he's a candidate for transoral surgical resection," he said. "I think patients really need to be presented with all the options. And we've got to acknowledge our biases and try to steer them to make a decision that's appropriate for the individual."

Photodynamic therapy was also mentioned as an option, but the consensus was that that approach required some refinement.

And the panel dismissed the idea of chemotherapy in early vocal fold cancer. "Nowadays, I think for medical–legal reasons it's impossible to propose such treatment for these patients," Dr. Brasnu said. "Morbidity is too high."

Dr. Weber agreed. "It's not something that I would do off a protocol," he said. "You have to remember when you look at the major trials, there's about a one to two percent mortality rate with chemotherapy. So I think you've got to be very careful about pursuing that." OT

A slightly different version of this appeared originally in 'ENToday,' another of the publications in Wolters Kluwer Health/Lippincott William & Wilkins' Targeted Publications group.