What Is CIN 2 and How Should It Be Treated?

The debate over whether cervical intraepithelial neoplasia grade 2 is a real, distinct entity continues.

BY ROXANNE NELSON
Contributing Writer

LAS VEGAS — Experts are divided on how aggressively cervical intraepithelial neoplasia grade 2 should be treated, and on whether observation is an acceptable option, especially in low-risk populations.

Cervical intraepithelial neoplasia (CIN) has been regarded as a preinvasive condition, with progressively higher grades being associated with an increasing risk of cancer. As most CIN 1 lesions regress without treatment, it has been suggested that CIN 2 may also have limited potential to progress to a more invasive disease.

"The goal of treatment for CIN is to prevent cancer by eliminating lesions with true malignant potential," Dr. Mark Spitzer said at a meeting of the American Society for Colposcopy and Cervical Pathology. "And we also want to avoid unnecessary treatment of lesions with little or no premalignant potential."

The data are mixed, said Dr. Spitzer of New York University, New York. Some studies show that CIN 2 is an intermediate entity that lies between CIN 1 and CIN 3 and has some premalignant potential although not as great as that of CIN 3. Other studies show that it is much closer to CIN 1 or benign disease, so it does not have real premalignant potential.

That raises the question, "Is the diagnosis of CIN 2 a reliable or reproducible diagnosis?" Dr. Spitzer said.

He pointed out that a few studies have assessed that question, and one concluded that interobserver variation is fair to good for the diagnosis of benign conditions, CIN 3, or invasive cancer, but poor for the diagnosis of CIN 1 or CIN 2. There is also poorer correlation between colposcopic and histologic diagnosis with CIN 2, compared with CIN 1 and CIN 3.

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"The problem with CIN 2 is that we don't really know what it is," Dr. Spitzer said. Any system of grading an intraepithelial lesion, in which there is a lesional continuum, is essentially artificial. A grading system that is based on light microscopy is subject to inter- and intraobserver variations in reporting, and treating all patients with CIN 2 will clearly result in the overtreatment of many of them.

There's also a question of age, when making the decision to treat cervical lesions. CIN 2 in adolescents is different than it is in adults, he explained. Some preliminary results showed that after 1 year, the behavior of CIN 2 in adolescents was the same as that of CIN 1.

"If you're under 20 the risk of invasive cancer is zero," said Dr. Spitzer. "If you're in the cohort under age 25, it still is really very low. So not treating CIN 2 in younger patients really makes a lot of sense."

However, Dr. Edward John Mayeaux Jr., an associate professor of family medicine and obstetrics and gynecology at Louisiana State University, Shreveport, disagreed with the assumption that CIN 2 isn't a real entity. "This has been debated before," he said, "And the data do show that it is different in its progression and regression potential than CIN 1. It has a biological activity that is different from both CIN 1 and CIN 3.

"In adolescents it is often transient and the risk of cancer is small, and our guidelines already say that observation for 1 year is acceptable for adolescents with CIN 2," Dr. Mayeux said.

Dr. Mayeaux also pointed out that in the United States, CIN 2 and 3 are managed in a similar fashion, primarily because the potential for progression is higher than that of CIN 1 and reliable histologic differentiation in CIN 2 and 3 is only moderate.

Overall, CIN 3 has about a 12% progression to cancer, but CIN 2 has about a 5% progression to cancer. These estimates do vary significantly, and at this time, most authors, guidelines, and professional organizations do recommend treatment for both CIN 2 and 3 lesions.

"We do need a better way to tell who is going to progress, and I agree with that," said Dr. Mayeaux. "The difference in our point of view is that I don't think we're there yet. And until we get there, we don't know what those changes are going to mean for patient outcome. We still need to treat it until we reach that point."

Given the current variations in equipment and practice, and the greater potential of CIN 2 to progress, compared with CIN 1, Dr. Mayeaux recommends no changes in current treatment protocols.

In rebuttal, Dr. Spitzer pointed out that while there is no doubt that CIN 2 has some premalignant potential, overtreatment with the loop electrosurgical excision procedure can also have consequences. ■

Drugs, Ultrasound May Be New Alternatives to Hysterectomy

BY GIANCARLO LA GIORGIA
Contributing Writer

TORONTO — Treating uterine fibroids may eventually be as simple as prescribing a pill, or zapping the benign growths with high-intensity focused ultrasound—two of several promising nonsurgical alternatives to the roughly 300,000 fibroid-related hysterectomies performed annually in the United States.

"[Hysterectomy] is the gold standard in fibroid treatment. … The problem is that it's a big operation, and the patient loses her uterus. For some women, that just is not an acceptable solution," said Dr. R. Torrance Andrews in an interview after his presentation at the annual meeting of the Society of Interventional Radiology.

Uterine fibroids, or leiomyomas, may cause infertility or premature delivery and in rare cases may become malignant. They affect about 30% of reproductive-age women, most commonly between the ages of 35 and 45 years, and particularly African American women, whose incidence rate is up to nine times higher than that of white women.

Dr. Andrews, chief of vascular and interventional radiology at the University of Washington Medical Center, Seattle, discussed mainstream fibroid treatments like hysterectomy, laparoscopic myomectomy, and uterine fibroid embolization (UFE), as well as emerging therapies like high-intensity focused ultrasound (HIFU), asoprisnil, and other methods.

In terms of recommending one treatment over the other, Dr. Andrews was frank: "I think it's a big mistake for interventional radiologists to tell patients authoritatively that they should have an embolization, instead of [a surgical] treatment.

"Similarly, unless a gynecologist is really well versed in embolization and patient selection, they should not tell patients that they are not embolization candidates. I think it needs to be a collaborative effort."

After hysterectomy, myomectomy and UFE are the main recommended fibroid therapies, both with their own benefits and disadvantages.

'The beauty of HIFU is that it's completely noninvasive. It's the "Star Trek" of medical intervention … and is going to have a very important role to play.'

Myomectomy is a targeted, surgical procedure that removes all visible fibroids and the symptoms they cause. However, recovery takes several weeks, and any abnormal tissue not seen during the procedure can grow back. Half of all myomectomy patients have fibroid recurrence within 5 years.

Fibroid embolotherapy offers more diffused, long-lasting treatment, with a recurrence rate of about 15% after 5-7 years. Patients typically experience painful cramps immediately after UFE and may have to wait for as long as 6 months for their fibroids to shrink enough to provide significant symptom relief.

Nevertheless, the outpatient procedure allows patients to return to their regular routine within a week after treatment.

HIFU was the next-generation therapy Dr. Andrews discussed at greatest length. It is a form of highly focused acoustic energy, delivered transcutaneously (without puncturing the skin) via an array of ultrasound transistors onto a single point within the body measuring 3 mm by 8 mm—about the size of a grain of rice.

In MR-guided HIFU procedures (granted FDA approval in 2004), the uterine region is scanned for fibroids and divided into planes at different depths.

All visible fibroid cells at a given depth are individually ablated before moving on to the next plane, and the process is repeated until the entire volume has been treated.

"The beauty of HIFU is that it's completely noninvasive. It's the 'Star Trek' of medical intervention … and is going to have a very important role to play, not just for fibroids, but for all kinds of tumors," Dr. Andrews said.

Despite its vaunted potential, Dr. Andrews said he knows of only a handful of U.S. centers offering HIFU treatment, and he attributes the scarcity to cost—about $1.5 million per unit—and to poor results to date.

"The published data on HIFU are terrible. The success rates are bad, partly because a quarter or more of patients drop out before they complete their treatment" he said, noting that not all patients will want to go through three or more 3-hour sessions inside a noisy, cramped MRI machine.

He also argued that the FDA's strict restrictions during trials—that investigators could not treat any fibroid within a centimeter and a half of normal uterine tissue—was "a guarantee for failure," and the main reason for the treatment's paltry 14% fibroid volume reduction.

His department at the University of Washington, which recently acquired an ultrasound-guided machine ("faster than MR, but not yet FDA-approved") for clinical study, has chosen not to offer any HIFU treatments until more data become available.

Dr. Andrews noted the buzz surrounding asoprisnil, a selective progesterone-receptor modulator that has been shown to significantly shrink fibroids and reduce their symptoms with minimal side effects during phase III trials. However, a new drug application, expected in late 2005, has not yet been filed with the FDA.

He also briefly discussed various thermal ablation techniques, developed mainly between 2000 and 2003. The basis of each is a transfer of energy—either laser, radiofrequency, microwave, or cryotherapy—through a percutaneous or transvaginal probe. They offer highly targeted delivery, but as with myomectomy, they only treat fibroids that can be seen. Dr. Andrews pointed out that interest in most of these techniques has largely faded away. ■