it’s not clear that [the surgery] is warranted outside the setting of a clinical trial."

An intergroup trial is testing this question, comparing chemotherapy and radiation followed by surgery with chemotherapy and radiation without surgery. But this trial is accruing patients slowly, according to Ruckdeschel.

"Unfortunately, preoperative treatment has become a religious issue, with some believing and some nonbelieving," he said. "But this trial needs to be completed, or modified so it can be completed, so we know whether to add the surgery."

**Up-and-Coming Drugs**

Whatever combination and sequence of chemotherapy, radiation, and surgery turns out to be most effective, a handful of up-and-coming new drugs may boost the effectiveness of combined therapies even more. Paclitaxel (Taxol®) and docetaxel (Taxotere®) both have shown activity in NSCLC, as have the camptothecins (e.g. topotecan), gemcitabine, and vinorelbine (Navelbine®). Several of these are now being tested in combination with cisplatin in phase II trials conducted by CALGB, Dillman said.

Biological agents, such as interleukin 2 and melatonin, may also be on the horizon, having produced high survival rates in Italian studies.

But the effects of newer treatments have yet to show up in survival statistics, and at the moment, the long-term CALGB data may be the best evidence that locally advanced lung cancer is susceptible to combined therapy. That in itself is welcome news. The new data do show, Dillman said, "that you don't have to give up on treatment of stage III lung cancer."

— Caroline McNeil

---

**Freezing Ovary Tissue May Help Cancer Patients Preserve Fertility**

A young woman is about to undergo cancer treatment that could leave her sterile, but knows she might want to have children in the future. She enters a fertility clinic, where she undergoes a simple surgical procedure in which tissue from one of her ovaries is removed. The tissue is then frozen, or cryopreserved, in liquid nitrogen at -198 degrees Celsius.

Two weeks later, recovered from surgery, the woman starts chemotherapy. A few years pass and she is told that it is safe for her to become pregnant but that the chemotherapy left her sterile. She returns to the fertility clinic where her thawed ovarian tissue is grafted onto a site next to the fallopian tubes. Within months, the ovarian tissue will be reassimilated and the woman will begin to ovulate normally, enabling her to produce children.

This scenario may sound like a science fiction plot, but scientists in a number of research groups around the world believe that this procedure, ovary cryopreservation, may be the next standard technique in fertility preservation. "I think this is definitely the way ahead," states Roger Gosden, M.D., of the Division of Obstetrics and Gynecology at the University of Leeds School of Medicine in England.

It may be especially useful for children and young women who are diagnosed with cancer and must undergo treatments — such as bone marrow transplantation, chemotherapy, or radiation — that will probably render them sterile.

Women and girls diagnosed with a cancer such as Hodgkin's disease, Wilms' tumor, or breast cancer have few, if any, options for preserving fertility. Some may retain a low level of fertility that enables them to give birth, but they often must resort to fertility clinics for assistance.

Others may opt to go through in vitro fertilization prior to receiving treatment, producing embryos to be frozen for future use. But for women with cancer, raising hormone levels or delaying treatment for at least 2 months of IVF cycles to ensure that enough ova are collected may be inadvisable or life threatening.

**Methods Unproven**

Others may choose to prevent the ovaries from being exposed to radiation by pinning them away from the radiation field, but scattered radiation can still cause damage. There is also a technique known as hormonal protection, in which the pituitary gland’s activity is suppressed and the function of the ovaries reduced in the hope that less damage will be done to inactive ovaries.

However, Gosden feels that this method and others have not necessarily
been proven effective. He believes it is better to totally remove the ovarian tissue from harm’s way.

Gosden, who leads the way in ovary cryopreservation research, believes that patients with the fewest options will be the ones to benefit the most from the new technique, such as young girls who are unable to go through IVF cycles and those who may not yet have a partner to provide sperm for IVF.

**Great Success**

Gosden has had great success in animal models. In studies using sheep, which have oocytes very similar to those of humans, the ovarian tissue was removed surgically and cryopreserved for 3 weeks. When thawed and grafted into the sheep near the opening of the fallopian tube, so that the eggs could easily travel down the reproductive tract, the ovarian tissue began to undergo revascularization. In a few months, the tissue began to produce ova on a regular cycle. Two of the original six sheep were mated within 3 to 4 months after having ovarian tissue returned, and each gave birth successfully.

In similar studies, the ovarian tissue of juvenile mice was removed, cryopreserved, and later thawed and grafted into sterilized host animals. Surprisingly, some of the tissue assumed a sphere-like shape similar to normal ovaries. After mating, many of the host females gave birth to normal offspring who were proven, by genetic markers, to have come from eggs from the transplanted ovarian tissue.

Experiments using mice with severe combined immunodeficiency disease (SCID) were also successful. In these studies, cryopreserved tissue from human ovaries was grafted into SCID mice. The ovarian tissue quickly began to function normally and produce mature ova. The survival rate for the primordial follicles, or egg-producing areas, ranged from 50% to 70% after being cryopreserved and thawed. Gosden and other researchers believe that similar rates will be achieved in humans.

The results of these and other studies conducted by Gosden led him to start a clinical trial of the technique with a small number of women in England. All have had ovarian tissue removed and cryopreserved, but none of the patients has yet had her ovarian tissue thawed and returned to her reproductive system.

Nonetheless, studies done to date have piqued the interest of several research groups worldwide, including a team at the Genetics and IVF Institute in Fairfax, Va.

**As Advertised**

Genetics and IVF has set up its own clinical trial for interested women, and its advertisement in the July 7 issue of *The New York Times Magazine* states that ovary cryopreservation is among the list of services immediately available at the institute. According to Mike Opsahl, M.D., a reproductive endocrinologist at the institute, it is probably the first clinic in the United States to offer this “innovative service.”

Genetics and IVF currently has four women enrolled in its clinical trial, with all costs being paid by the patients themselves. The protocol, which is apparently based on Gosden’s, is limited to adults with cancer but may be expanded to include children.

In 1996, 11.8% of all women diagnosed with cancer will be of childbearing age. This is about 70,000 women, but not all of those women may need to seek a treatment such as ovary cryopreservation. Each type of cancer is treated differently and individual treatments may not affect fertility.

The process could also be used by disease-free women who wish to preserve their ovarian tissue for later use, although Genetics and IVF is not promoting this option. A woman’s oocytes may begin to lose fertility potential when she is in her late 30s, but according to Opsahl, a woman can have a normal pregnancy well into her 50s. So a woman of 20 could undergo the procedure and then in her late 40s have the tissue replaced, conferring on her the fertility properties of a 20-year-old. In effect, the woman has “stopped time” for her ovaries.

**Viable Option**

Such uses for ovary cryopreservation raise many ethical questions. However, researchers must first see if the procedure works for the women who are enrolled in clinical trials. Opsahl believes the institute’s first patient will be ready to have her ovarian tissue returned in the next 1 to 3 years.

Both Opsahl and Gosden are confident that this technique will work and will be a viable option to offer women faced with sterilizing medical treatments before they are ready to surrender the possibility of having children.

“This technique aims to restore natural fertility,” said Gosden, “but the work is still at an early stage, and it shouldn’t be offered as a routine treatment.” He also cautioned that ovary cryopreservation “is not a panacea” and that it may not work for some patients such as older women who already have reduced fertility before having ovarian tissue removed.

— Catherine Law