

## Gynecology

## Decision to intervene

By Hubert Filser



Source: Jan Greune

**Surgery and the benefits of thoroughness: Gynecologist Sven Mahner talks about the critical importance of surgical approaches in the treatment of gynecological cancers.**

Probably only a surgeon would define the physician's weapons in the battle against life-threatening cancers so deftly and directly: "Steel, rays and drugs are the keystones of our whole strategy," says gynecologist Sven Mahner, Director of the Department of Gynecology and Obstetrics at the LMU Medical Center. Mahner specializes in the treatment of gynecological cancers, tumors of the ovary, uterus, cervix, vagina and the breast. The steel of course stands for the surgical removal of tumors, the rays for the treatment of tumor cells with X-rays and other forms of radiation, and the drugs are those used in cancer therapy. And indeed, that effectively encompasses the contents of our anti-cancer arsenal. But perhaps one must take such an abstract view of the challenge in order to be able to deal with the clinical and scientific issues with which Mahner is daily confronted in his efforts to provide the best possible treatment for his patients.

He also refers to his set of therapeutic strategies as a *Dreiklang* – a (musical) triad. His use of the term would seem to evoke the need to find a 'harmonious' balance between the demands of patient care, clinical routine and biomedical research that confront clinical researchers. Mahner treats patients who have gynecological cancers, dispenses advice, prescribes drugs, and performs

operations – while having to keep up the latest advances in fields such as immunotherapy, and teach courses. "I don't actually regard it as a balancing act," he says. "I see it more as an opportunity, a chance to translate new insights into everyday practice as soon possible, so as to improve patient care." No two cancer cases are the same, each patient's history is unique, he points out, and this view of cancer is clearly reflected in the interaction between basic research and clinical care. The closer the interaction between the two, the better the patient's chances, he affirms.

Appraisal of the efficacy of candidate drugs for the treatment of cancers usually involves large-scale, randomized clinical studies – partly because the market for new drugs is of interest to the pharmaceutical industry. "But we are now beginning to reap the benefits of advances in evidence-based medicine, which provide a realistic picture of the prospects," says Mahner. He is of course acutely aware – not least on the basis of the data from gynecologic oncology centers all over the world – of the central role of surgery in the treatment of cancer. And here he comes back to his triad, and to the debate to which his own work contributes: How can the different components of his strategy be most effectively combined? What is the optimal relationship between them? Which blend

of methodologies is best for which patient and what stage of disease? How can chemotherapy best enhance the impact of each of the other elements? This is a debate that centers on quantitative data, as precise knowledge of statistical significances and survival rates enables research programs to be properly designed and therapies to be reliably evaluated.

### Surgery and survival rates

"Irrespective of the type of cancer, it is tremendously important that all of the diseased tissue be excised," Mahner says. The surgeon must be "meticulous and thorough," otherwise the enemy will return to the field. Particularly in the case of ovarian cancer, survival rates are critically dependent on the quality of the surgical intervention. The surgeon's job is to locate and remove every last one of the often widely scattered satellite tumors, he stresses. Studies undertaken at oncology centers worldwide, and large-scale meta-analyses of data relating to the efficacy of chemotherapy, show that – provided that the tumor has been completely removed and the patient then receives chemotherapy – the 5-year survival rate for ovarian cancer is just under 70%. However, if tumor cells remain in the body, that rate sinks dramatically – to around 25%.

## Research

Mahner is convinced of the potential of surgery in this area, and of the necessity to strive for, and establish the highest possible standards. It doesn't take long for him to ask if I have any idea of what surgeons are confronted with. He takes out his laptop and shows me pictures used in one of his lectures for his students. They show ovaries with obviously abnormal growths. But that's not all. Metastatic tumors have established themselves in the peritoneum, the womb, the spleen, parts of the intestine and the liver. One can make out small incrustations and pale nodes. In each of these regions, the tumor tissue takes a different form, appearing as bulbous or reticulate excrescences, well-defined and whitish, or hidden in the well perfused tissues of the gut. Surgeons often must decide in the course of the operation itself what needs to be removed. "Don't be alarmed," he remarks, "the patient is in good shape." – A complicated operation like this can take up to 8 hours, and it is important that one takes one's time, he adds. The surgeon must be fit and highly motivated, and he must believe in what he is doing. "But a good surgeon alone is no great help to the patient," he says. He needs an experienced interdisciplinary team. Only with the whole-hearted support of anesthesiologists, urologists and abdominal surgeons, well-trained nurses and state-of-the-art technology can one consistently achieve optimal results for patients.

Mahner plans to focus on the issue of the quality of surgery in the context of the international Trial on Radical Upfront Surgical Therapy (TRUST) in advanced ovarian cancer. Some 700 patients will be enrolled in the study. Its goal is to determine whether surgery immediately upon diagnosis followed by chemotherapy is a more effective approach

than surgery bracketed by two courses of chemotherapy.

### Two hours? Not enough for difficult cases

"We really shouldn't have to carry out this study at all," Mahner tells me, "for two large-scale international studies have already addressed this issue." However, the results were quite chastening, primarily because of the low survival rates achieved. This led some to ask whether factors, such as poor selection of participants or poor overall quality of the surgical interventions, might not have played a role in the sobering outcome. The average duration of operations was not much more than 2 hours. "In my opinion," Mahner comments, "complicated operations in cases of ovarian cancer cannot be adequately performed in 2 hours." And only if the operations have been carried out with the requisite care and thoroughness, can one compare surgical with chemotherapeutic outcomes, he adds. For this

reason, only centers that carry out an extensive quality assurance process, allow for external auditing and perform at least 36 such operations per year will participate in the new TRUST study.

Unless one is an expert, it can be difficult to assess the quality of clinical studies. There is an acknowledged need for properly conducted studies in this area, but it is often difficult to find the necessary financial resources. Neither public funding nor drug companies have so far had much interest in funding evaluations of the efficacy of surgical procedures. Nevertheless, TRUST was initiated by the Study Group formed by the German Working Group (*Arbeitsgemeinschaft*) on Gynecological Oncology (AGO) and is now recruiting patients. It is expected to take a decade to acquire final results of this study. But useful guidelines can only be formulated on the basis of methodologically reliable clinical studies. – But 10 years is a long time. "It is theoretically possible that within the next decade a drug will appear



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## Research

on the market that is more efficacious than any operation," Mahner muses. "In that case, the study would be terminated."

### Setbacks and disappointments

Oncologists live in hope that new drugs will in future play a larger role in the effective treatment of malignancies. In recent years, immunologists have made notable progress in exploiting advances in the understanding of tumorigenesis for therapeutic purposes. However, immunotherapies have in the past run into unexpected obstacles. "Methodologies that worked spectacularly in the laboratory turned out to help only very small subgroups of patients," Mahner explains. This was because the lab results were valid only for particular genetic constellations. Patients are genetically diverse, and so are their tumors. "We must learn to identify those groups of patients who are most likely to benefit from a given drug or therapeutic regime, even if these groups turn out to be small," Mahner

says. "And where the genetic findings argue against its use, we could then avoid needlessly subjecting patients to the stresses of chemotherapy."

Sometimes, all the very best doctors can do is to slow the progression of the disease. A great deal is now known about the involvement of various combinations of genes in specific types of cancers. Patients who have inherited certain mutant variants of the genes *BRCA1* and *BRCA2* from one parent have a higher risk of developing cancers of the breast and the ovary. This is because a subsequent mutation that knocks out the second copy of the gene in either tissue will initiate tumorigenesis. However, cells that are mutant for both copies of either *BRCA1* or *BRCA2* are also vulnerable, as their ability to activate the appropriate repair mechanisms in response to DNA damage is reduced. Indeed, molecular biologists have shown that inhibition of PARP – enzymes involved in triggering DNA repair – causes such cells to undergo

programmed cell death. "Inhibition of the repair mechanisms kills the cancer cell," says Mahner.

Last October, an international research collaboration, including members of the AGO Study Group, published the results of a Phase III clinical trial in which ovarian cancer patients were given Niraparib, which inhibits both PARP enzymes, as a maintenance therapy following successful chemotherapy. In the control group the median period of progression-free survival was 5.5 months, while in those who received the drug it was 21.5 months. "The results surprised us," says Mahner, who led the German arm of the study, which was published in the highly respected *New England Journal of Medicine*. "The treatment delayed recurrence of the cancer by a factor of 4. That's a tremendous improvement. Advances like these, in surgery and pharmacology, can significantly increase the arsenal available to us in the fight against gynecological tumors.

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