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INTERVIEW DR. GHADJAR
JAMA ONCOLOGY JOURNAL

1. The EORTC 62961-ESHO 95 Trial was completed in November 2006. Why is JAMA Oncology only reporting now and what is the significance?

Long term data of the **EORTC 62961-ESHO 95 trial** comparing neoadjuvant chemotherapy vs. neoadjuvant regional hyperthermia plus chemotherapy for patients with **localized high-risk soft tissue sarcoma** was published by **Issels et al.** in February 2018 based on a median **follow-up of 11.3 years**. The recruitment of the total number of **341 patients** was conducted from July 1997 to November 2006. The database for this analysis was closed in December 2014. The long follow-up duration is necessary to analyze potential differences in the secondary trial endpoint of overall survival. The significance of the results is that the **addition of regional hyperthermia did not only improve local progression-free survival but also significantly improved overall survival** as compared to neoadjuvant chemotherapy alone.

2. But why has it taken so long to publish the results?

Issels et al. closely analyzed their data after the database was closed. Due to the **unique and convincing data**, the manuscript was then submitted to **high-impact** medical journals and the process of manuscript review, re-submission and revision took time until the manuscript was accepted for publication by *JAMA Oncology*.

3. Is it true the study was prematurely halted? Were there negative results?

No, the predefined analysis plan as stated in the trial protocol was followed. The early trial results were published in *Lancet Oncology* in 2010, reporting that the **primary trial endpoint local progression-free survival was significantly improved** by neoadjuvant

regional hyperthermia plus chemotherapy vs. neoadjuvant chemotherapy alone based on a median **follow-up of 34 months**. As the primary trial endpoint was significantly improved (as far back as 2010) the trial had to be regarded as a positive one. In 2010 the follow-up duration was not sufficient to detect potential differences in overall survival. Eight years later this has changed, and **a significant overall survival benefit could be detected in favor of regional hyperthermia**.

4. Soft tissue sarcoma accounts for less than 1% of all malignancies. Are the findings really that important for cancer patients?

Yes, because the principle of **using heat to improve the effectiveness of chemotherapy can be translated into treatment schedules of other cancer types** that are currently only treated with dismal cure rates. One example is **primary resectable pancreatic cancer**, which is usually treated by surgery followed by adjuvant chemotherapy. The **HEAT trial** is a randomized Phase III trial comparing adjuvant chemotherapy alone vs. adjuvant regional hyperthermia plus chemotherapy (Clinical Trials.gov identifier: NCT01077427). Another example – inter alia – is the treatment of **ovarian cancer recurrences**. Here the Nordostdeutsche Gesellschaft für Gynäkologische Onkologie (**NOGGO**) is about to launch a randomized Phase II trial to compare chemotherapy alone vs. regional hyperthermia plus chemotherapy for platinum sensitive recurrences. The recent results of Issels et al. are definitively encouraging to test the value of hyperthermia for other cancer disease sites in order to improve the effectiveness of currently available treatments.

5. What are you hoping to achieve with this?

The results published by Issels et al. suggest a **substantial median overall survival benefit of 9.2 years** (6.2 years for neoadjuvant chemotherapy alone vs. 15.4 for neoadjuvant chemotherapy plus regional hyperthermia). For 12 regional hyperthermia sessions costs of approximately **12 x 2,500 EUR** must be calculated. These costs appear **relatively low when compared to novel drugs like immune checkpoint inhibitors**, which can easily cost many times more without leading to a comparable overall survival benefit. Therefore, **regional hyperthermia appears to be an effective, well tolerated and relatively cheap treatment**.

6. Has there been progress in cancer treatment since 2006? Could we expect even more from this approach?

With regard to the treatment of high-risk soft tissue sarcoma there has been, unfortunately, no significant progress since 2006. Today's more advanced techniques involving **image-guided radiotherapy** may improve both tolerance and effectiveness. Results using **external beam radiotherapy** in the neoadjuvant setting from non-randomized studies, as well as results expected from the recently completed randomized trial on surgery with or without radiation therapy in patients with previously untreated nonmetastatic retroperitoneal STS (**STRASS**) should form the basis for future trials with the addition of RHT.

7. Does equipment matter? What are the requirements for good treatment, leading to therapeutic results like in the *JAMA Oncology* publication?

From what we know it is important to reach temperatures of ≥41-42°C within the tumor. This is easier to achieve in **sarcomas of the extremities and pelvic region** rather than within the abdomen. It is important to measure the temperature within the tumor either by a direct thermal probe placed within the tumor or for pelvic tumors by indirect surrogate measurements via body orifices, such as the rectum, vagina or urethra. Temperature measurements during hyperthermia treatments can **guide the treatment** and are important for **quality assurance** purposes. Based on **computed tomography** patient/tumor anatomy information it is possible and recommended with commercially available software to **pre-plan the specific absorption rate (SAR) distribution** within the treatment volume of interest.

Thank you for taking the time to talk to us.

Dr. Ghadjar was speaking to Monica Sennewald, Dr. Sennewald Medizintechnik GmbH

Hyperthermia Improves Survival In Soft Tissue Sarcoma

JAMA Oncology | Original Investigation

Long-term results of a randomized clinical trial

SOFT TISSUE SARCOMA IN THE US

NEW CASES 5,670
DEATHS 2,380

NEW CASES 7,370
DEATHS 2,770

According to the American Cancer Society 13,040 new Soft Tissue Sarcoma cases will be diagnosed in the United States in 2018.

9 HYPERTHERMIA CENTERS

Germany: University Hospital Munich-Grosshadern of the LMU
Argirov Clinic Starnberger See
Rotkreuz Krankenhaus Munich
Essen University Hospital
Düsseldorf University Hospital
Charité – Universitätsmedizin Berlin
Austria: University Hospital Graz
Norway: Haukeland University Hospital, Bergen
USA: Duke University Hospital, Durham

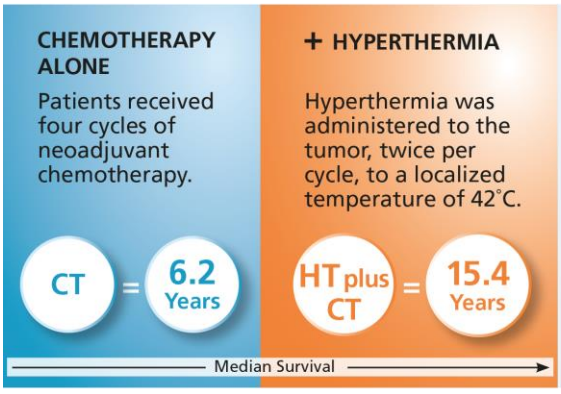
HYPERTHERMIA EQUIPMENT

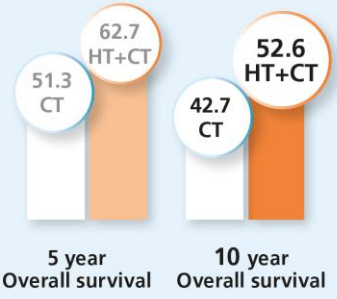
Provided by Pyrexar Medical
Line of Radiative Hyperthermia Systems

TRIAL PARTICIPANTS

RESULTS

After a median follow-up of 11.3 years, patients who received chemotherapy plus hyperthermia had prolonged median survival rate of 15.4 years compared with those randomized to neoadjuvant chemotherapy alone (6.2 years).





23%
Improvement of 10 year survival by addition of hyperthermia

Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma
The EORTC 62961-ESHO 95 Randomized Clinical Trial

Issels RD, Lindner LH, Verweij J, Wessalowski R, Reichardt P, Wust P, Ghadjar P, Hohenberger P, Angele M, Salat C, Vujaskovic Z, Daugaard S, Mella O, Mansmann U, Dürr HR, Knösel T, Abdel-Rahman S, Schmidt M, Hiddemann W, Jauch K, Belka C, Gronchi A. Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma The EORTC 62961-ESHO 95 Randomized Clinical Trial.
JAMA Oncol. Published online February 15, 2018. doi:10.1001/-jamaoncol.2017.4996