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The place and role of clinical hyperthermia in oncological thermotherapy: let's define what we are talking about

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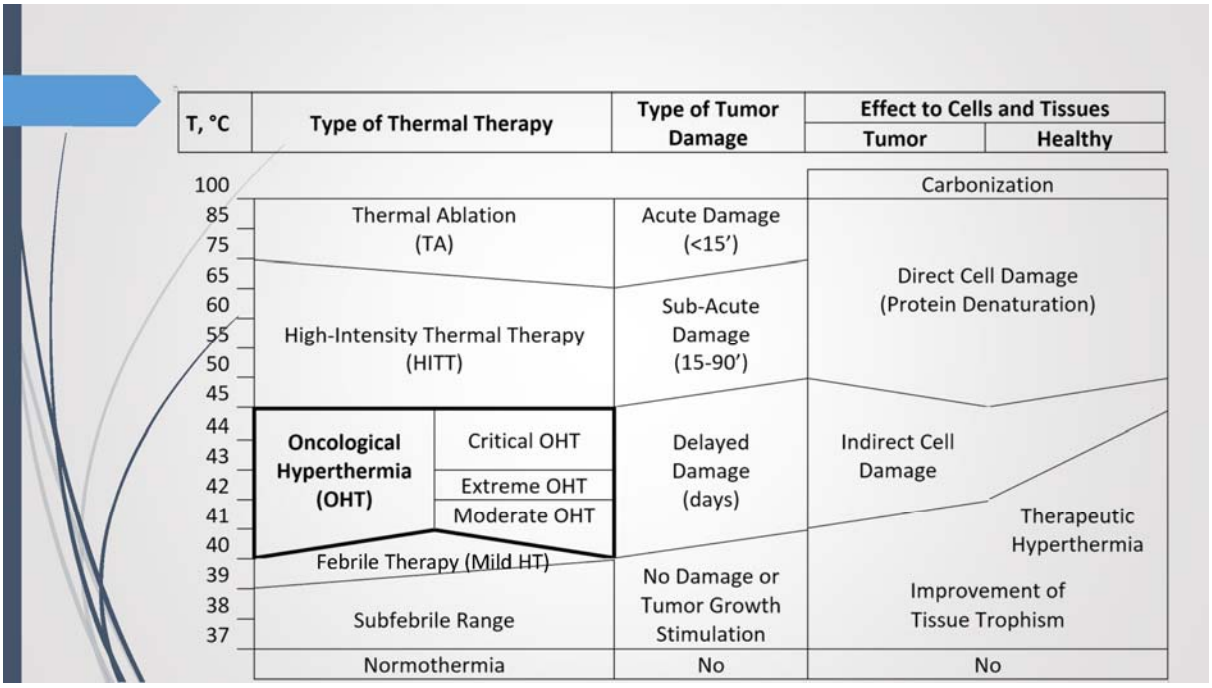
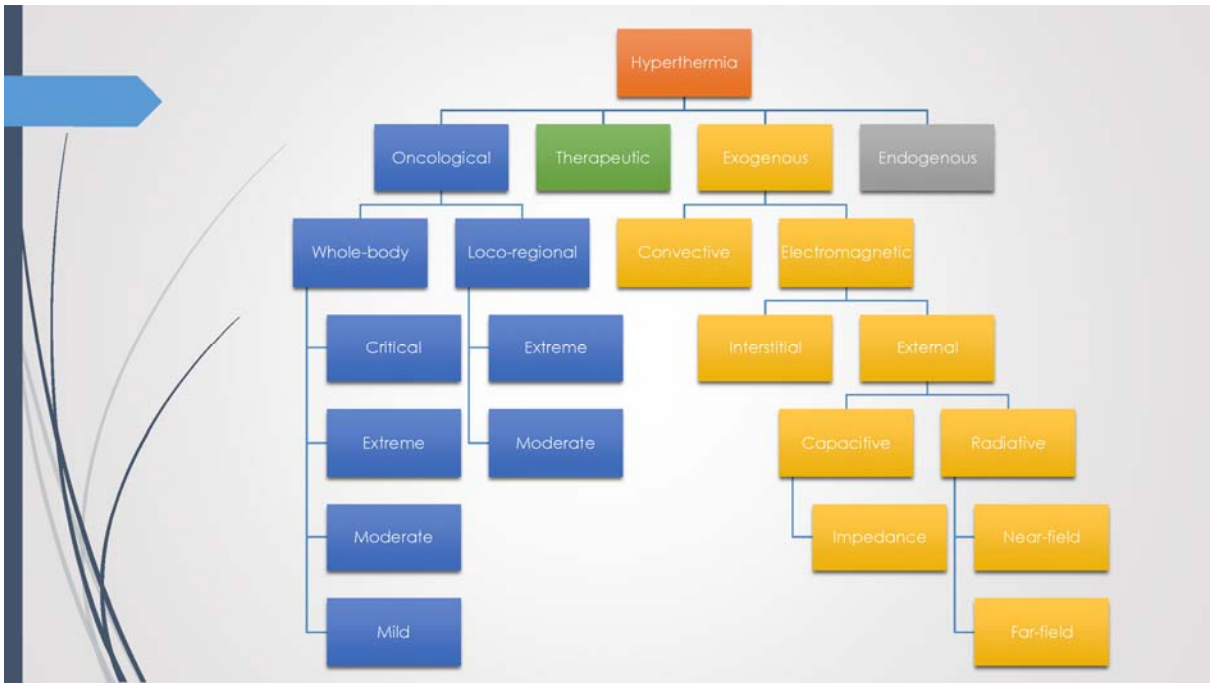
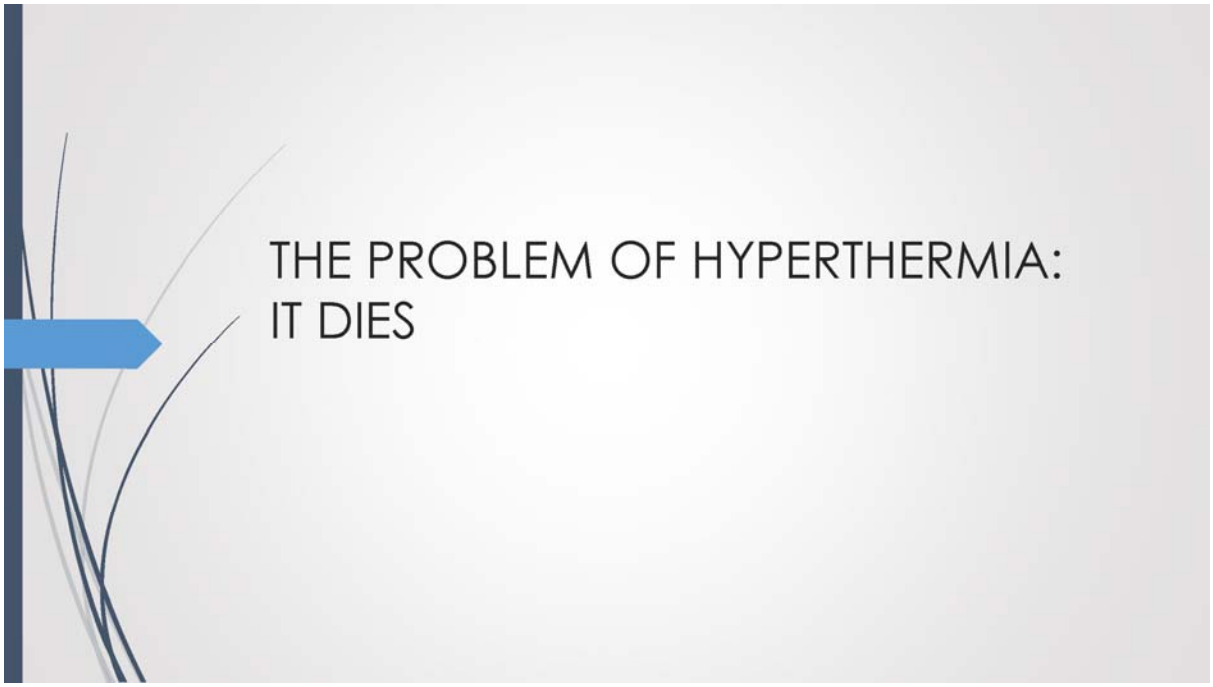
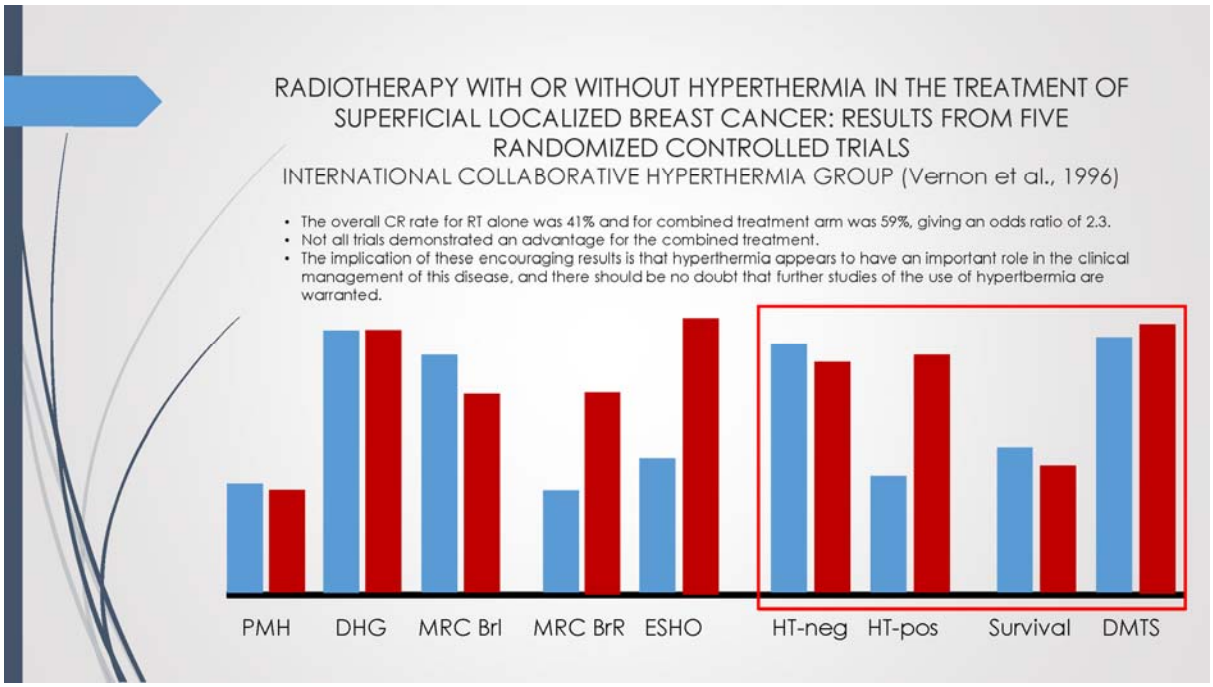
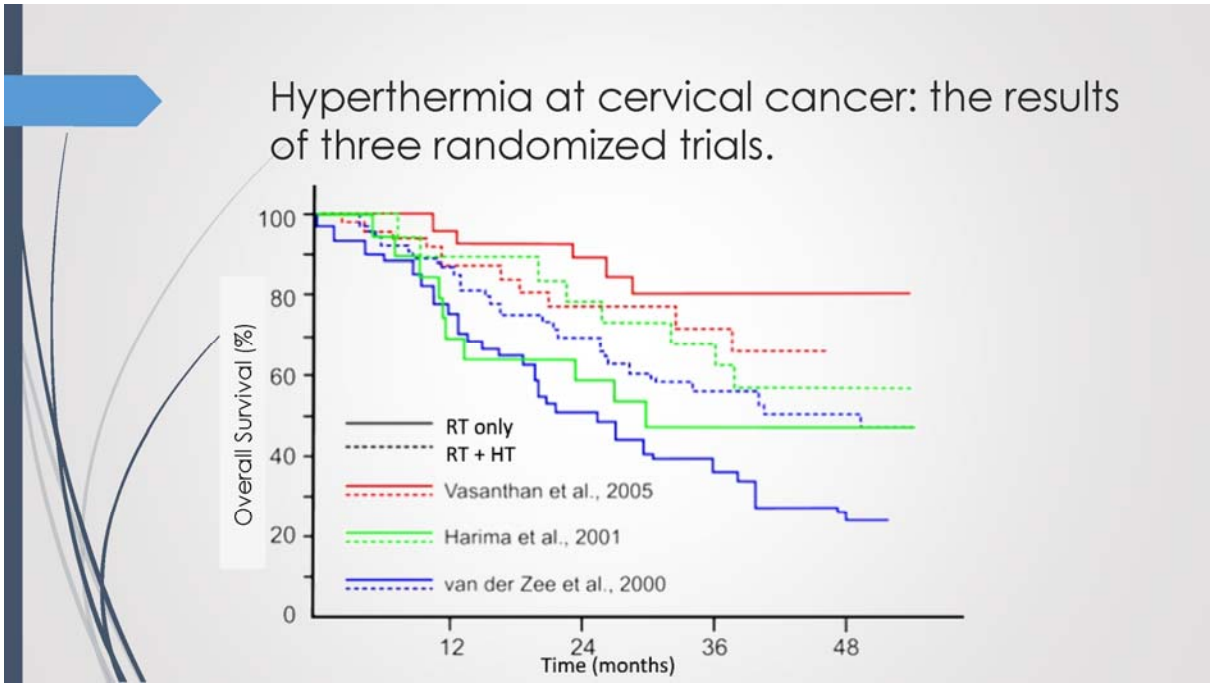
34th Annual Conference of the International Clinical Hyperthermia Society
Pesaro, Italy
22nd September 2016




Hyperthermia
Oncological
Therapeutic
Exogenous
Endogenous
Whole-body
Loco-regional
Convective
Electromagnetic
Critical
Extreme
Extreme
Moderate
Moderate
Mild
Interstitial
External
Capacitive
Radiative
Impedance
Near-field
Far-field

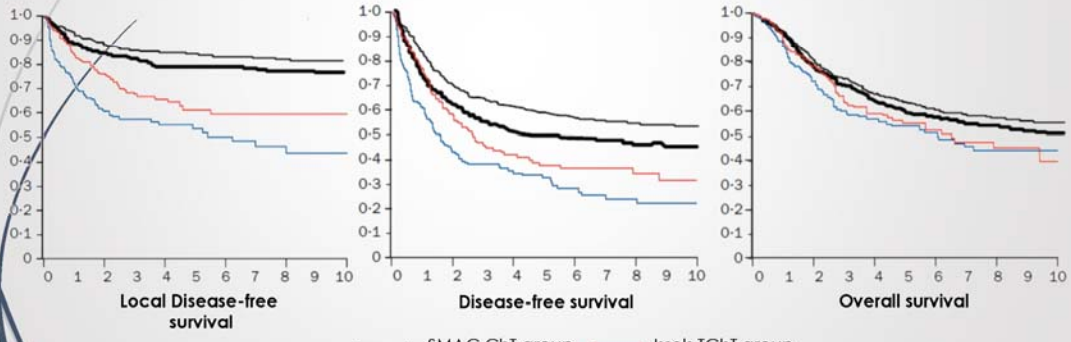

THE PROBLEM OF HYPERTHERMIA:
IT DIES


RADIOTHERAPY WITH OR WITHOUT HYPERTHERMIA IN THE TREATMENT OF SUPERFICIAL LOCALIZED BREAST CANCER: RESULTS FROM FIVE RANDOMIZED CONTROLLED TRIALS
INTERNATIONAL COLLABORATIVE HYPERTHERMIA GROUP (Vernon et al., 1996)
• The overall CR rate for RT alone was 41% and for combined treatment arm was 59%, giving an odds ratio of 2.3.
• Not all trials demonstrated an advantage for the combined treatment.
• The implication of these encouraging results is that hyperthermia appears to have an important role in the clinical management of this disease, and there should be no doubt that further studies of the use of hypertbermia are warranted.
PMH
DHG
MRC Brl
MRC BrR
ESHO
HT-neg
HT-pos
Survival
DMTS


Hyperthermia at cervical cancer: the results of three randomized trials.
Overall Survival (%)
100
80
60
40
20
0
12
24
36
48
Time (months)
RT only
RT + HT
Vasanthan et al., 2005
Harima et al., 2001
van der Zee et al., 2000

Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study (Issels et al., 2010)

To our knowledge, this is the first randomised phase 3 trial to show that regional hyperthermia increases the benefit of chemotherapy. Adding regional hyperthermia to chemotherapy is a new effective treatment strategy for patients with high-risk STS, including STS with an abdominal or retroperitoneal location.



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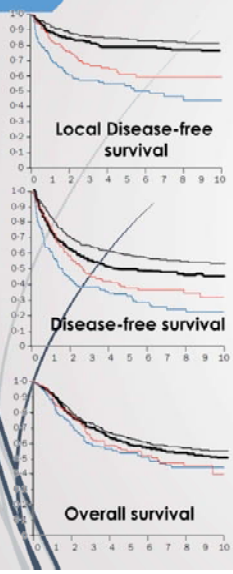

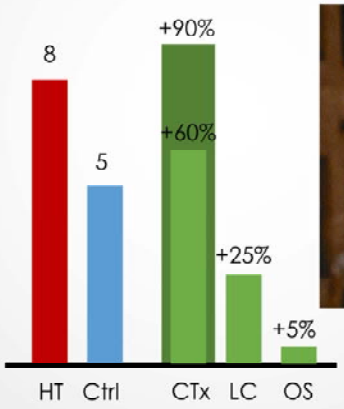

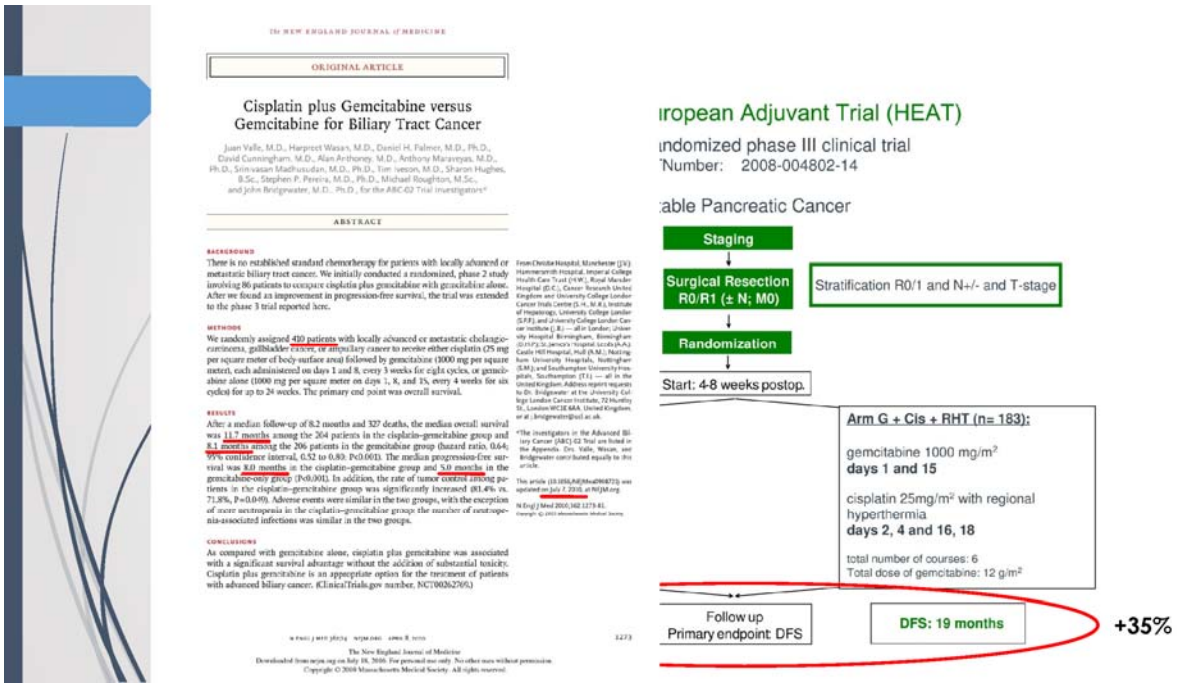

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

Juan Valle, M.D., Harpreet Wasan, M.D., Daniel H. Palmer, M.D., Ph.D., David Cunningham, M.D., Alan Anthoney, M.D., Anthony Maraveyas, M.D., Ph.D., Srinivasan Madhusudan, M.D., Ph.D., Tim Iveson, M.D., Sharon Hughes, B.Sc., Stephen P. Pereira, M.D., Ph.D., Michael Roughton, M.Sc., and John Bridgewater, M.D., Ph.D., for the ABC-02 Trial Investigators*

ABSTRACT

BACKGROUND

There is no established standard chemotherapy for patients with locally advanced or metastatic biliary tract cancer. We initially conducted a randomized, phase 2 study involving 86 patients to compare cisplatin plus gemcitabine with gemcitabine alone. After we found an improvement in progression-free survival, the trial was extended to the phase 3 trial reported here.

METHODS

We randomly assigned 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer to receive either cisplatin (25 mg per square meter of body-surface area) followed by gemcitabine (1000 mg per square meter), each administered on days 1 and 8, every 3 weeks for eight cycles, or gemcitabine alone (1000 mg per square meter on days 1, 8, and 15, every 4 weeks for six cycles) for up to 24 weeks. The primary end point was overall survival.

RESULTS

After a median follow-up of 8.2 months and 327 deaths, the median overall survival was 11.7 months among the 204 patients in the cisplatin–gemcitabine group and 8.1 months among the 206 patients in the gemcitabine group (hazard ratio, 0.64; 95% confidence interval, 0.52 to 0.80; P<0.001). The median progression-free survival was 8.0 months in the cisplatin–gemcitabine group and 5.0 months in the gemcitabine-only group (P<0.001). In addition, the rate of tumor control among patients in the cisplatin–gemcitabine group was significantly increased (81.4% vs. 71.8%, P=0.049). Adverse events were similar in the two groups, with the exception of more neutropenia in the cisplatin–gemcitabine groups; the number of neutropenia-associated infections was similar in the two groups.

CONCLUSIONS

As compared with gemcitabine alone, cisplatin plus gemcitabine was associated with a significant survival advantage without the addition of substantial toxicity. Cisplatin plus gemcitabine is an appropriate option for the treatment of patients with advanced biliary cancer. (ClinicalTrials.gov number, NCT00026676.)

From Christie Hospital, Manchester (J.V.); Hammersmith Hospital, Imperial College Health Care Trust (H.W.), Royal Marsden Hospital (D.C.), Cancer Research United Kingdom and University College London Cancer Trials Centre (S.-H., M.-K.), Institute of Hepatology, University College London (S.P.P.), and University College London Cancer Institute (J.B.) — all in London; University Hospital Birmingham, Birmingham (D.H.P.); St. James's Hospital, Leeds (A.M.); Castle Hill Hospital, Hull (A.M.); Nottingham University Hospitals, Nottingham (S.M.); and Southampton University Hospitals, Southampton (T.I.) — all in the United Kingdom. Address reprint requests to Dr. Bridgewater at the University College London Cancer Institute, 72 Huntley St., London WC1E 6AA, United Kingdom, or at j.bridgewater@ucl.ac.uk.

*The investigators in the Advanced Biliary Cancer (ABC)-02 Trial are listed in the Appendix. Drs. Valle, Wasan, and Bridgewater contributed equally to this article.

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N Engl J Med 2010;362:1273-81.

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1273

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ıropean Adjuvant Trial (HEAT)

ındomized phase III clinical trial
'Number: 2008-004802-14

:able Pancreatic Cancer

Staging

Surgical Resection R0/R1 (± N; M0)

Stratification R0/1 and N+/- and T-stage

Randomization

Start: 4-8 weeks postop.

Arm G + Cis + RHT (n= 183):

gemcitabine 1000 mg/m²
days 1 and 15

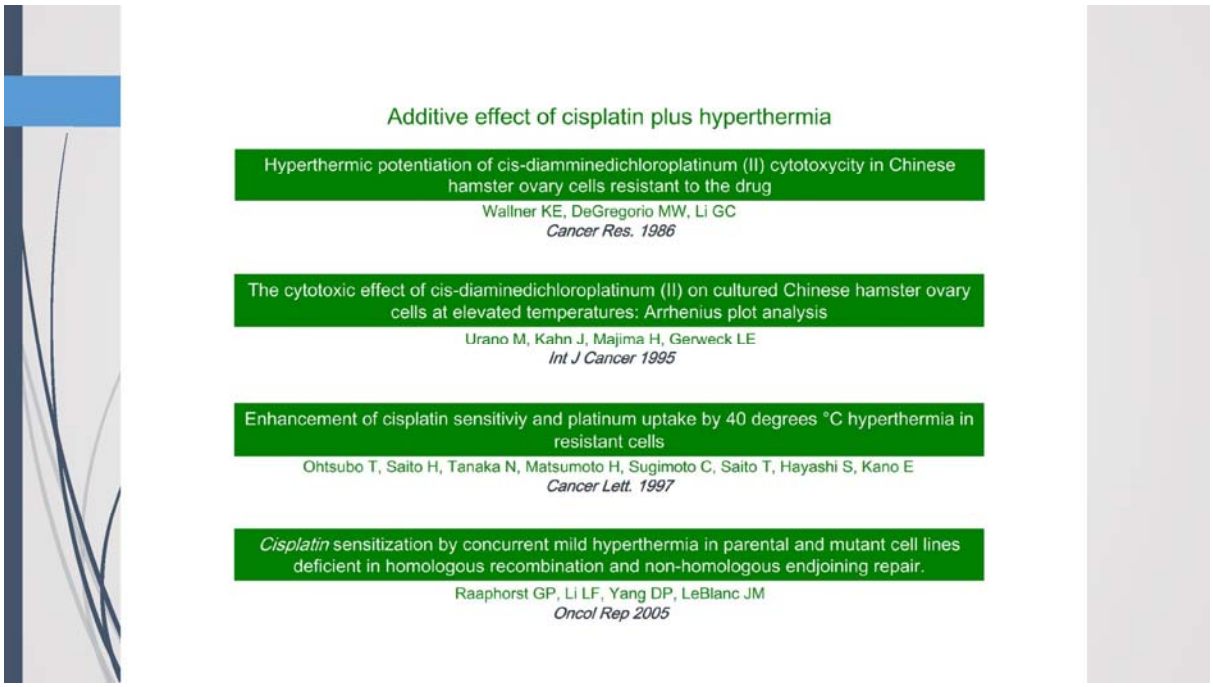
cisplatin 25mg/m² with regional hyperthermia
days 2, 4 and 16, 18

total number of courses: 6
Total dose of gemcitabine: 12 g/m²

Follow up
Primary endpoint: DFS

DFS: 19 months

+35%



Additive effect of cisplatin plus hyperthermia

Hyperthermic potentiation of cis-diamminedichloroplatinum (II) cytotoxycity in Chinese hamster ovary cells resistant to the drug

Wallner KE, DeGregorio MW, Li GC
Cancer Res. 1986

The cytotoxic effect of cis-diaminedichloroplatinum (II) on cultured Chinese hamster ovary cells at elevated temperatures: Arrhenius plot analysis

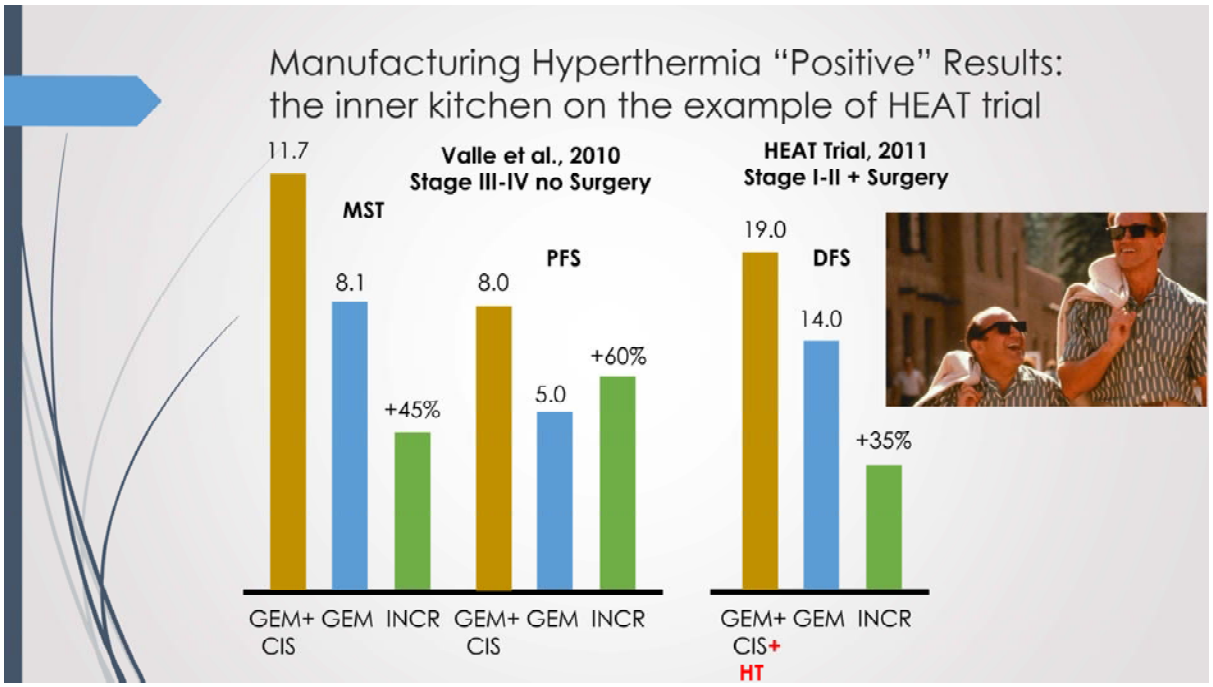
Urano M, Kahn J, Majima H, Gerweck LE
Int J Cancer 1995

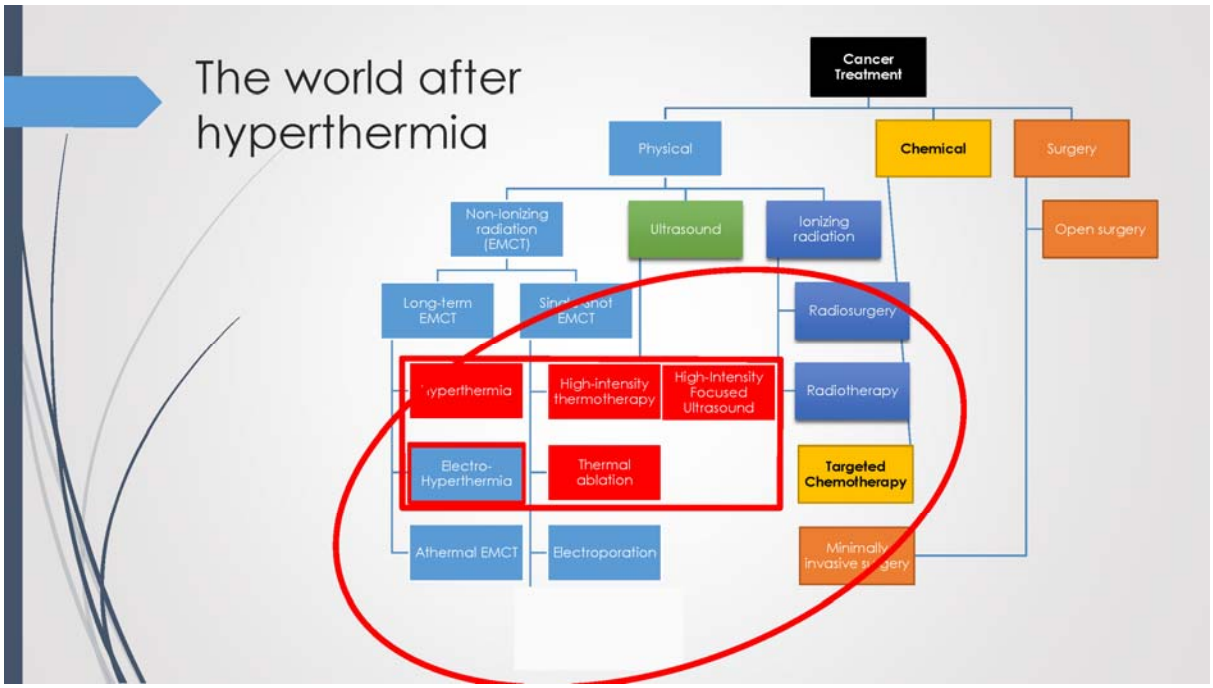
Enhancement of cisplatin sensitiviy and platinum uptake by 40 degrees °C hyperthermia in resistant cells

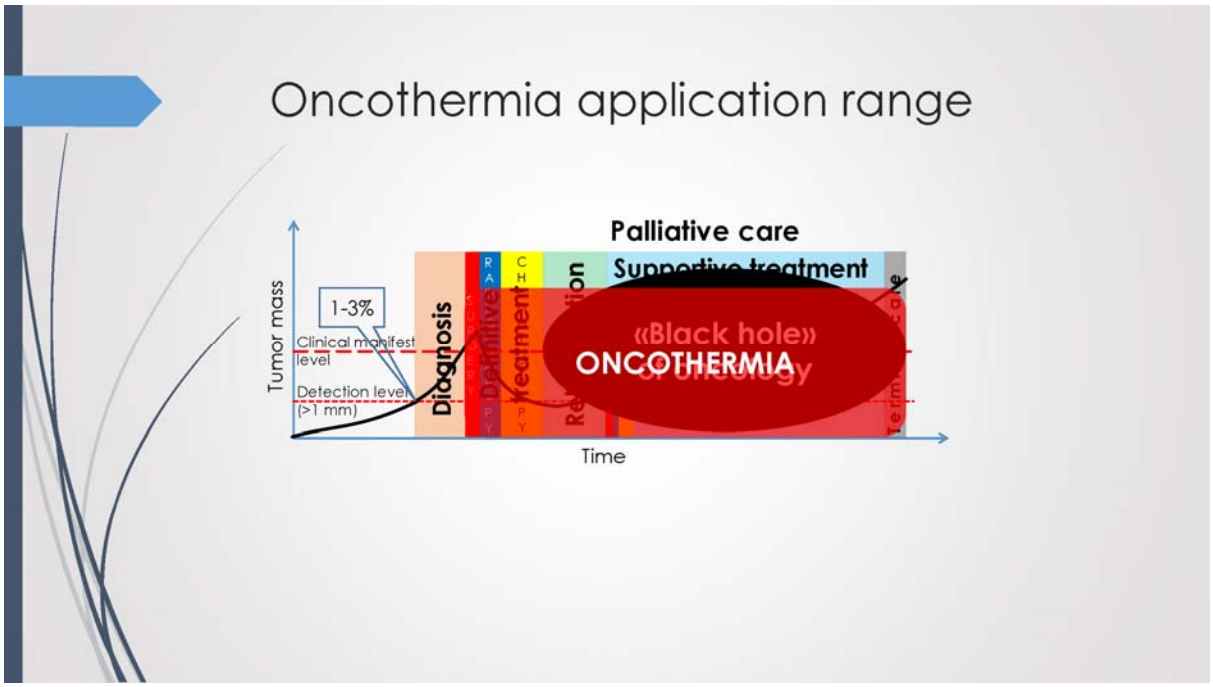
Ohtsubo T, Saito H, Tanaka N, Matsumoto H, Sugimoto C, Saito T, Hayashi S, Kano E
Cancer Lett. 1997

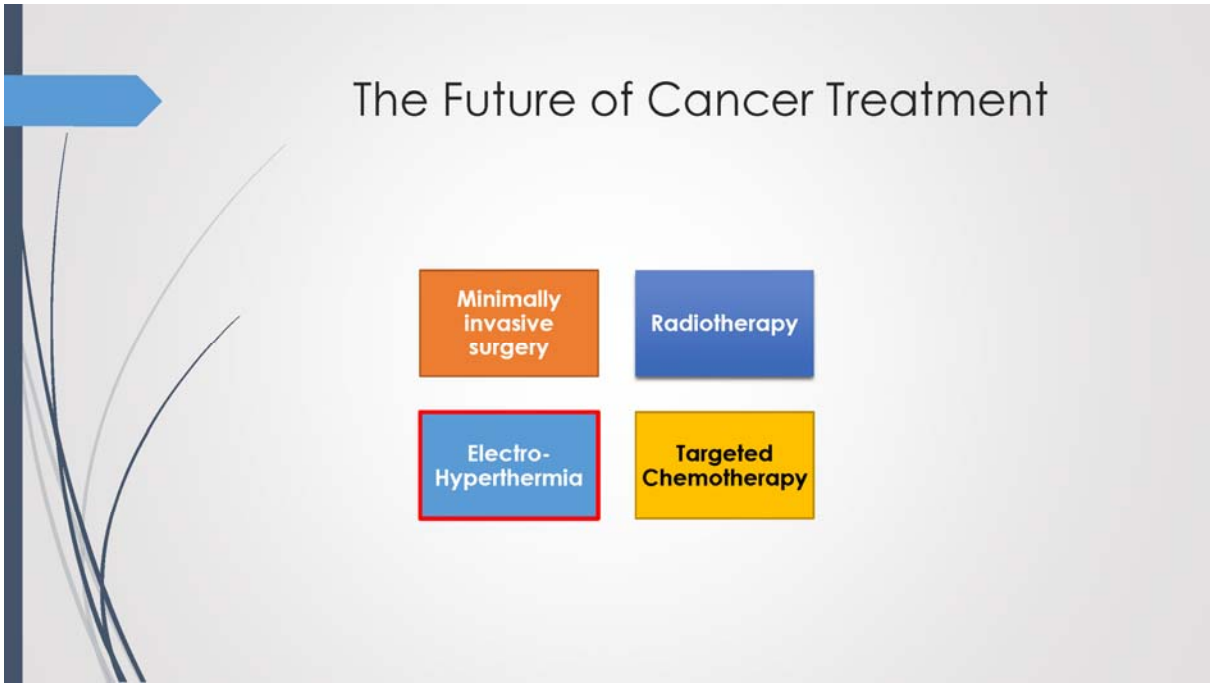
Cisplatin sensitization by concurrent mild hyperthermia in parental and mutant cell lines deficient in homologous recombination and non-homologous endjoining repair.

Raaphorst GP, Li LF, Yang DP, LeBlanc JM
Oncol Rep 2005


Manufacturing Hyperthermia "Positive" Results:
the inner kitchen on the example of HEAT trial
Valle et al., 2010
Stage III-IV no Surgery
MST
PFS
11.7
8.1
+45%
8.0
5.0
+60%
GEM+ CIS
GEM
INCR
GEM+ CIS
GEM
INCR
HEAT Trial, 2011
Stage I-II + Surgery
19.0
DFS
14.0
+35%
GEM+ CIS+ HT
GEM
INCR


The world after hyperthermia
Cancer Treatment
Physical
Chemical
Surgery
Non-Ionizing radiation (EMCT)
Ultrasound
Ionizing radiation
Open surgery
Long-term EMCT
Radiosurgery
Hyperthermia
High-intensity thermotherapy
High-Intensity Focused Ultrasound
Radiotherapy
Electro-Hyperthermia
Thermal ablation
Targeted Chemotherapy
Athermal EMCT
Electroporation


Oncothermia application range
Palliative care
Supportive treatment
Tumor mass
1-3%
Clinical manifest level
Detection level (>1 mm)
Diagnosis
Treatment
«Black hole»
ONCOTHERMIA
Time


The Future of Cancer Treatment
Minimally invasive surgery
Radiotherapy
Electro-Hyperthermia
Targeted Chemotherapy

Thank you for attention

Huilgol trial

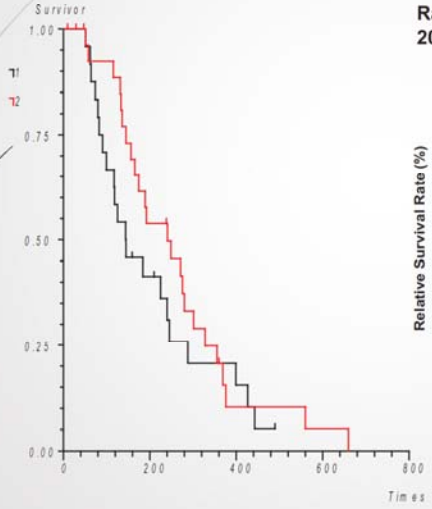
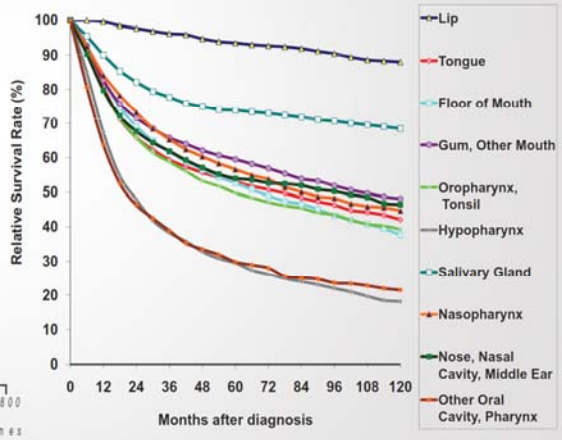


Figure 2.1: Cancer of the Head and Neck: Relative Survival Rate (%) by Primary Site, Ages 20+, 12 SEER Areas, 1988-2001



Huilgol trial

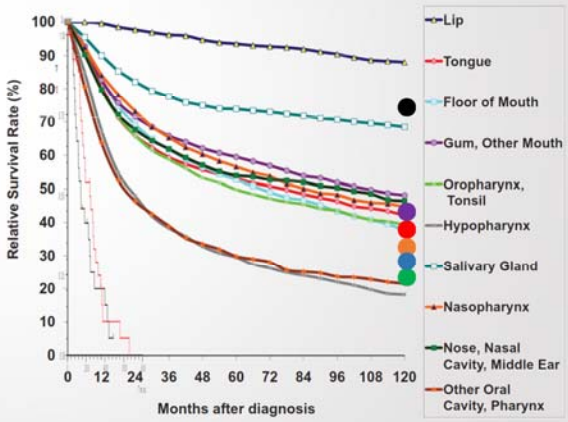
"The 5-year relative survival rates were 74.5% for the lip, 42.7% for the anterior tongue, 25.5% for the posterior tongue, 45.1% for the mouth, 29.7% for the oropharynx, 38.7% for the nasopharynx, 29.1% for the hypopharynx, and 41.2% for the larynx." (Mumbai 1987-1991).

Yeole BB, Sankaranarayanan R, Sunny M Sc L, Swaminathan R, Parkin DM. Survival from head and neck cancer in Mumbai (Bombay), India. Cancer. 2000 Jul 15;89(2):437-44.

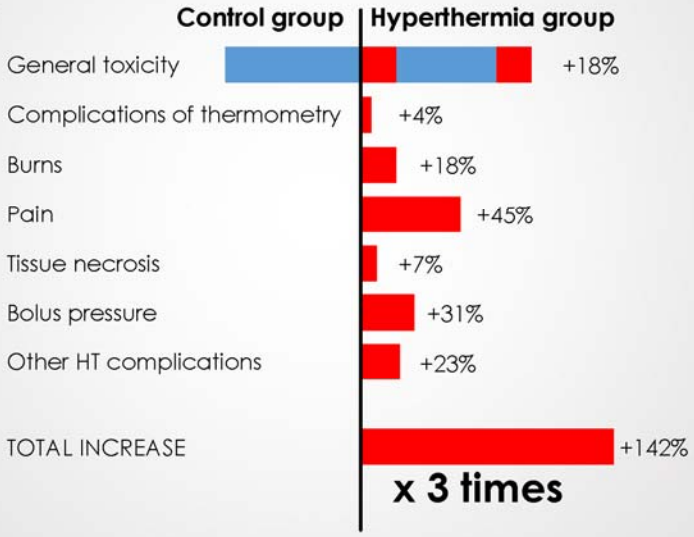
"The overall 5-year survival rate was in the range of 20-43% for oral cancer, 8-25% for pharyngeal cancers and 25-62% for laryngeal cancer." (Mumbai, 1987-1989; 25% of stage IV).

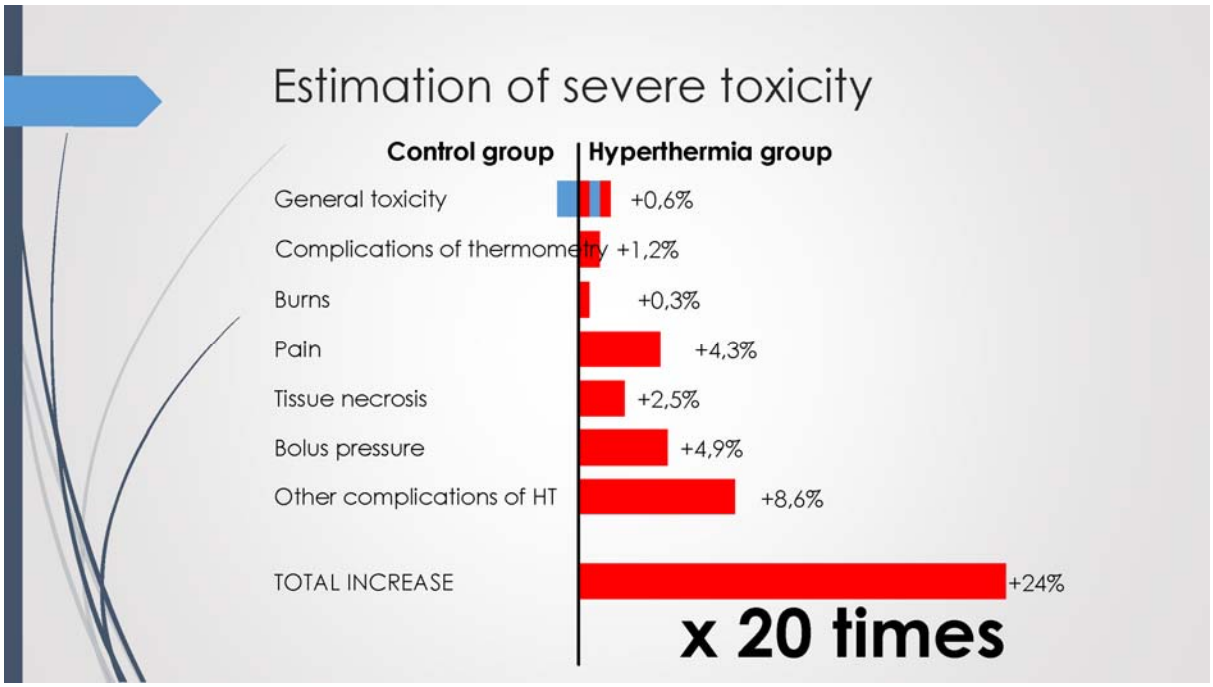
Rao DN, Shroff PD, Chattopadhyay G, Dinshaw KA. Survival analysis of 5595 head and neck cancers--results of conventional treatment in a high-risk population. Br J Cancer. 1998 May; 77(9): 1514–1518.

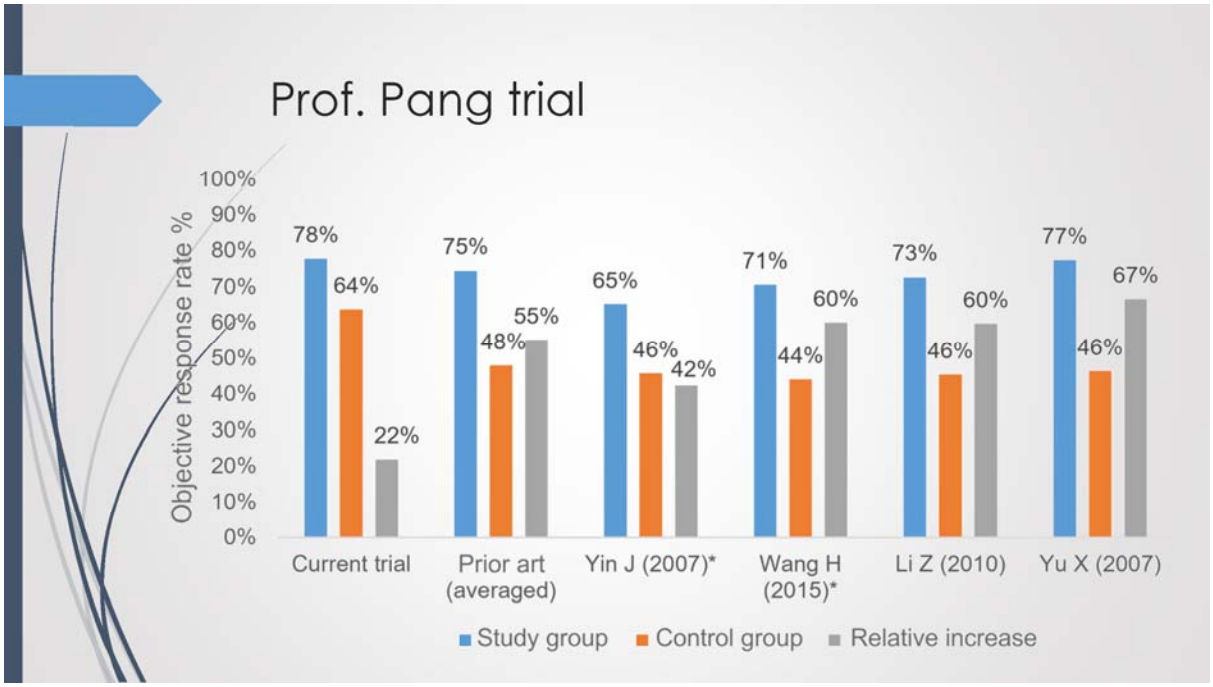
Figure 2.1: Cancer of the Head and Neck: Relative Survival Rate (%) by Primary Site, Ages 20+, 12 SEER Areas, 1988-2001

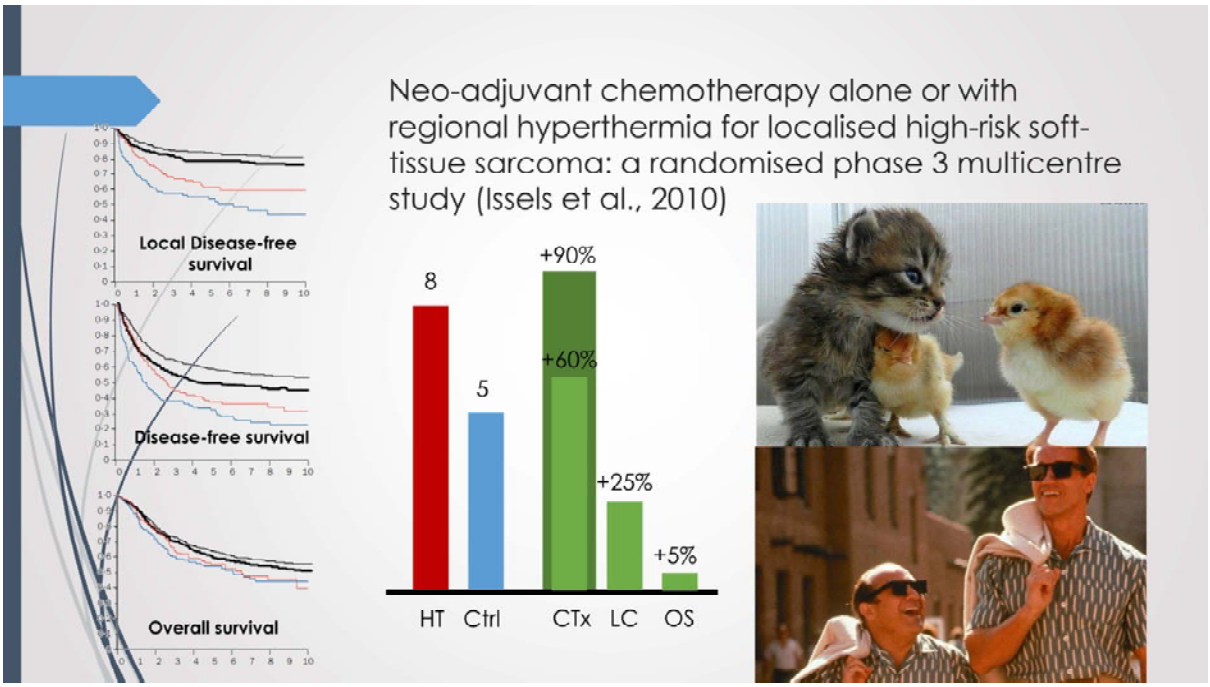


Estimation of general toxicity

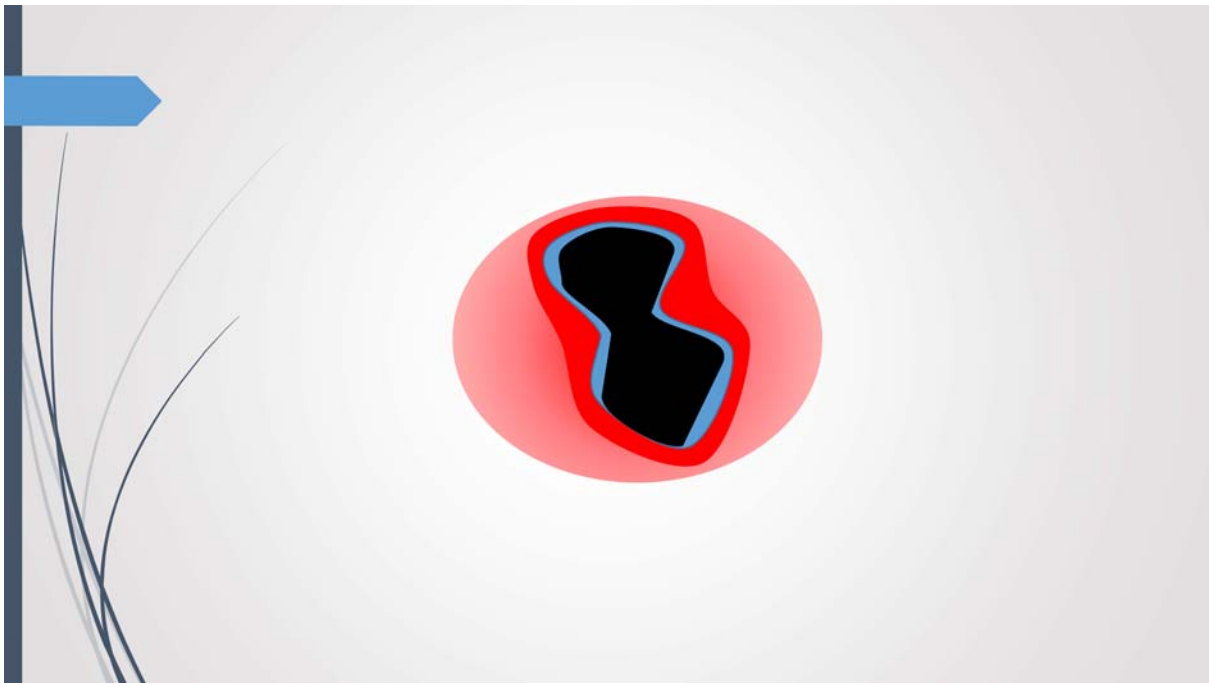


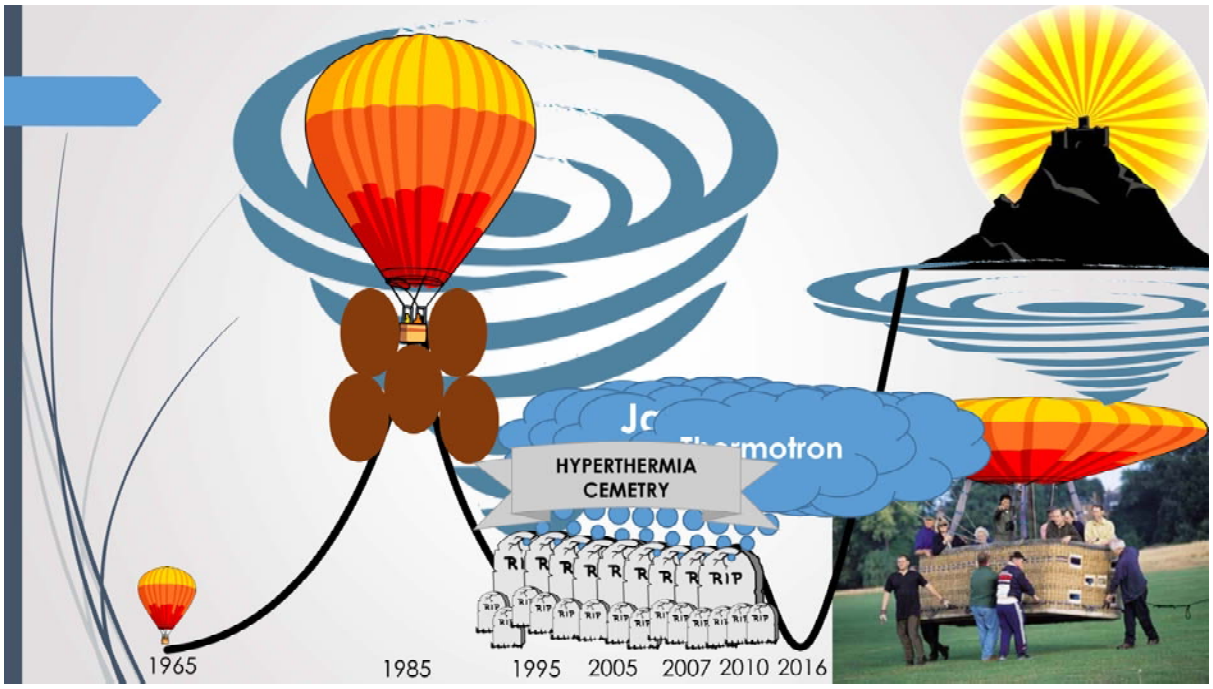

Estimation of severe toxicity
Control group
Hyperthermia group
General toxicity
+0,6%
Complications of thermometry
+1,2%
Burns
+0,3%
Pain
+4,3%
Tissue necrosis
+2,5%
Bolus pressure
+4,9%
Other complications of HT
+8,6%
TOTAL INCREASE
+24%
x 20 times


Prof. Pang trial
Objective response rate %
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
78%
64%
22%
75%
48%
55%
65%
46%
42%
71%
44%
60%
73%
46%
60%
77%
46%
67%
Current trial
Prior art (averaged)
Yin J (2007)*
Wang H (2015)*
Li Z (2010)
Yu X (2007)
Study group
Control group
Relative increase


Local Disease-free survival
Disease-free survival
Overall survival
Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study (Issels et al., 2010)
8
5
+90%
+60%
+25%
+5%
HT
Ctrl
CTx
LC
OS


Where is hyperthermia?
International Congress of Hyperthermic Oncology
Physiology
microwave RF Cryotherapy
Thermoradiotherapy Treatment Planning
Ultrasound Thermal Medicine
immunology Thermochemotherapy
Gene Expression Fever metabolism
MRI Laser inflammation
ablation HIFU Signal Transduction
Nanoparticles
Thermal Therapy: Hot Science, Cool Medicine and All That Jazz
New Orleans, April 11-15, 2016




HYPERTHERMIA
CEMETRY
RIP
1965
1985
1995
2005
2007
2010
2016