Radiotherapy and the role of hyperthermia in breast cancer

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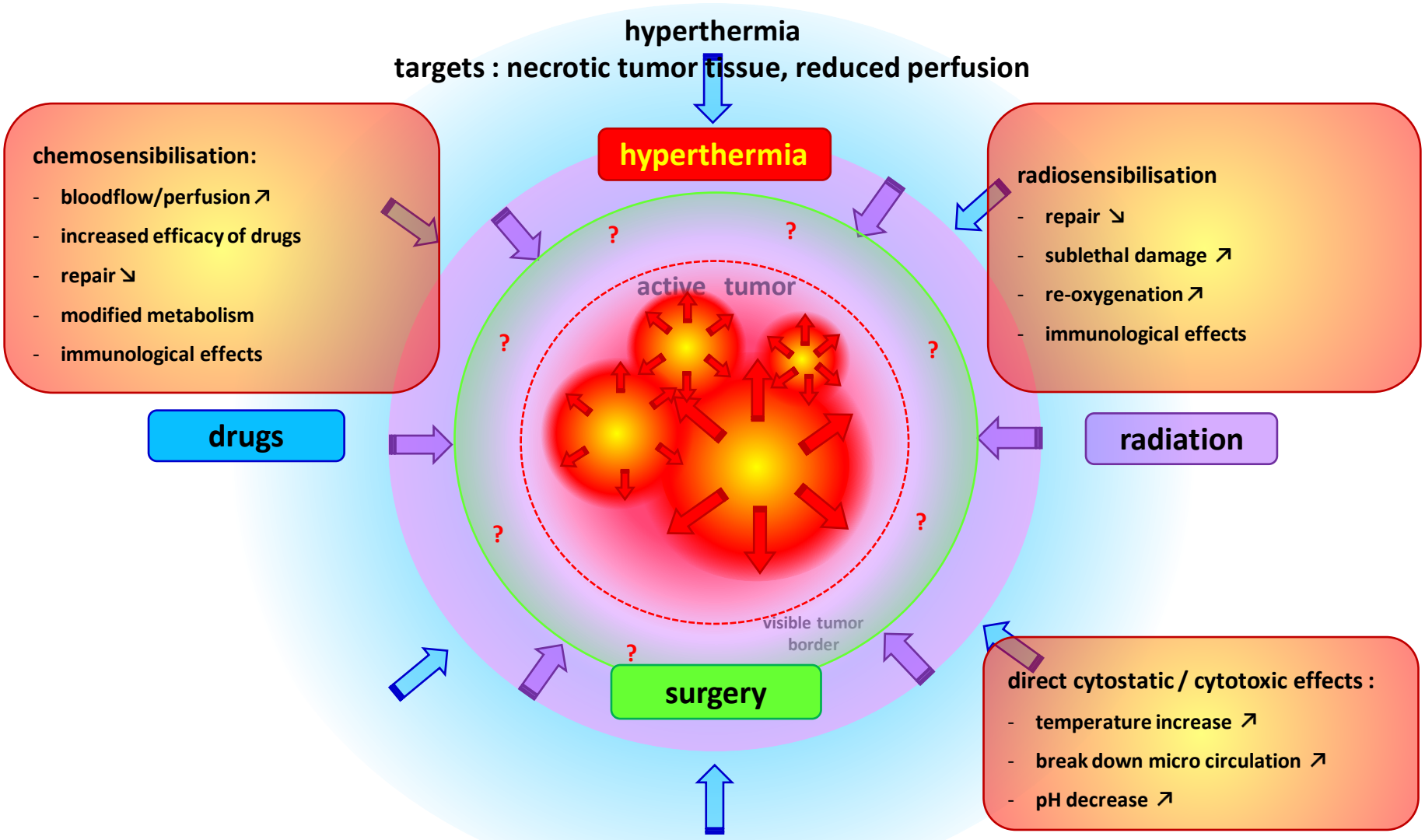
Radiotherapy and the role of hyperthermia in breast cancer
Radiosensibilisation



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Radiotherapy and the role of hyperthermia in breast cancer
Introduction (1)

- **Breast Cancer Statistics: In 2020, about 2.3 million women were diagnosed with breast cancer worldwide and 685'000 died.**
- **Due to screening, early diagnosis etc. there is an increasing number of breast conserving treatments (BCT).**
- **That means in most of breast cancer cases local treatment consists of surgery & radiotherapy with fair good local control**
- **Recently: in early breast cancer stage (pT1/small pT2 <3cm, pN0 M0 G1-2 ER+ PR+) and age > 65 years RT can even be omitted in BCT, but with the prize of a tenfold increase of local recurrence (9.5% vs 0.9%). (see Kunkler ICH et al, Conserving Surgery with or without Irradiation in Early Breast Cancer. N Engl J Med 2023 F; 388 (7): 585-594.)**
- **→ it looks like, that the addition of hyperthermia as a radiosensitizer is not really needed….**

Radiotherapy and the role of hyperthermia in breast cancer
Introduction (2): locally recurrent breast cancer (LRBC)

- Limits - in a horrible way – quality of life during life time
- ….decaying tumor with odor, special wound care, social isolation etc.

- "…this is a very rare event…"
- "…such patients we never see here…"

- That means, these patients „disappear" completely, are no longer listed in any statistics, almost nobody knows about them

- Can we estimate, how many women are suffering from such a disaster?

local recurrence 30.11.2018: PD inspite of chemotherapy

1996 1. breast cancer right, pT1 pN0 M0, BCT with RT/hormono-T;
2008 2. breast cancer left, pT1b pN0 M0, BCT with RT/hormono-T;
3/2018 local recurrence in both breasts
4/2018 bilateral mastectomy
5 – 10/2018: adjuvant chemotherapy, local tumor progression

8.8.2019: after x chemotherapies….

8.12.2018: Letrozol, progression,
12.1.2019: Palbociclib, progression,
8.2. – 4.4.2019 : Capicitabine/Vinorelbine, progression,
16.4.2019: Avastin, Eribulin, progression,
4.6.201: CBDCA 2x, progression,
29.7.2019: Epirubicin, progression

Radiotherapy and the role of hyperthermia in breast cancer
Introduction (3): locally recurrent breast cancer (LRBC)

- **Locoregional control and survival has been improved due to advances in screening, diagnostic imaging and better systemic treatments. However, the 5-year locoregional recurrence rate (LRR) rate is 2.5% – 3.5%.**

- **Despite the relative low rate of failure, the absolute number of LRR is increasing due to the growth in the absolute number of breast cancer patients and breast conserving treatments (BCT).**

- **If in future RT will be broadly omitted in early BC and elderly patients, LRR rate will increase even more**

- **Local treatment of local recurrence is usually salvage mastectomy after initial breast conserving therapy or local excision after initial mastectomy.**

Radiotherapy and the role of hyperthermia in breast cancer
Introduction (4): locally recurrent breast cancer (LRBC)

- **LRBC patients with high risk characteristics, e.g., rpT2-4 (tumor size) or rpN+ (lymph node involvement) or R1-2 (radicality of resection) or V1 (blood vessel infiltration) or L1 (lymphangiosis) or negative hormonal receptors or all of this have an indication for postoperative (re-)irradiation after surgery in order to improve locoregional control and survival. (Buchholz et al. 2020, Poortmans et al. 2017, Kaidar-Person et al. 2018, Clemons et al. 2001, van Tienhoven et al. 2005).**

- **In case of re-irradiation (re-RT) total RT-doses are limited and, therefore, superficial hyperthermia (sHT) can be added to improve results with less toxicity.**

- **In The Netherlands combined postoperative sHT & re-RT is a standard procedure and in single-arm retrospective studies 3-year locoregional controls ranges from 68% to 83% (Linthorst et al. 2013, Oldenborg et al. 2010).**

- **A meta-analysis of previously irradiated patients showed an average complete response of 62% in unresectable LRR compared to 38% after irradiation alone (Datta et al. 2016).**

Radiotherapy and the role of hyperthermia in breast cancer
Introduction (5): locally recurrent breast cancer (LRBC)

→ „infirmity“ in locally uncontrolled breast cancer…

cancer en cuirasse (7/2023):
progression despite radiotherapy, chemotherapy, re-irradiation

- remains a very intensive therapeutic challenge
- means enormous efforts in patient care
- care is done in dermatologic, gynecologic or oncologic offices, clinics or palliative stations, hospices, often without any coordination of different care options, eventually at home done by family
- “out of any therapy”? …or not ?
- re-irradiation with reduced doses combined with superficial hyperthermia offers a (last) the possibility (i) to achieve local control again, or (ii) to distinctly relieve pain, ulceration, bleedings, thoracic constriction, lymphœdema, nerve infiltration etc.

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Radiotherapy and the role of hyperthermia in breast cancer
Results: locally advanced/recurrent breast cancer

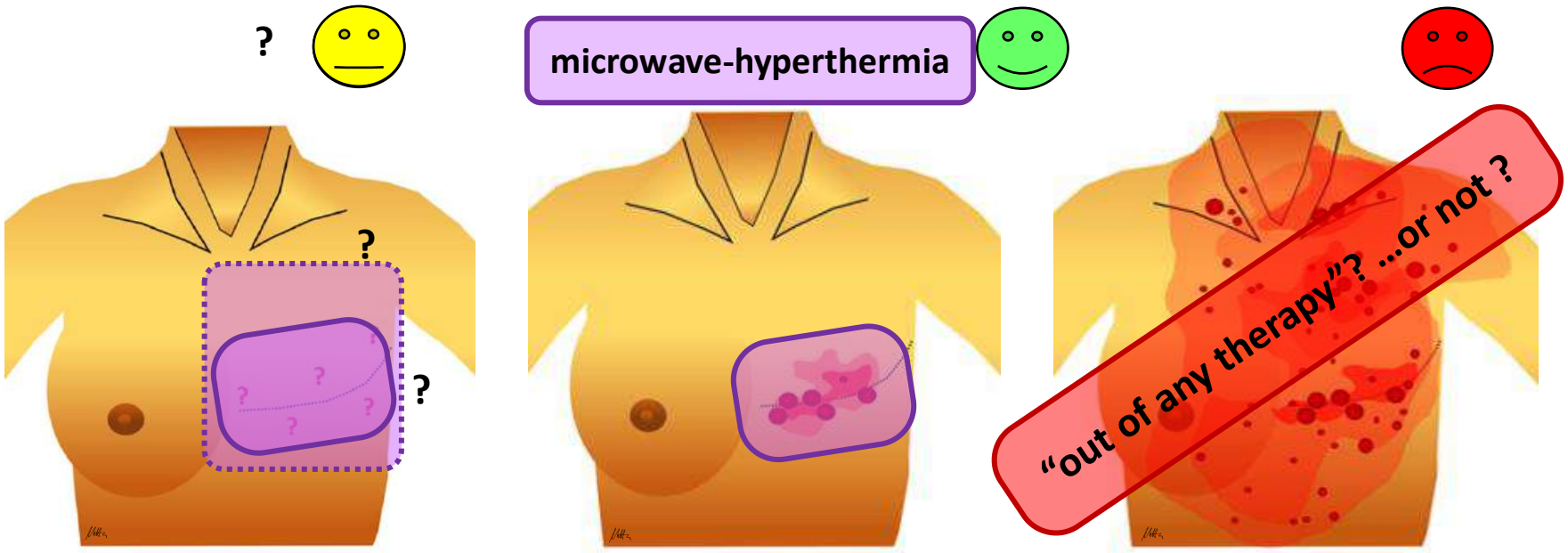
Autors	n	HT technique	Total RT-dose (Gy)	CR /local control	HT related toxicity ≥ G2
a. randomised trials					
Vernon et al., 1996	56	100 – 1000 MHz	32	38 % (RT) 78% (HT-RT)	23%
Jones et al., 2005	39	434 MHz	30 – 66	24 % (RT) 68% (HT-RT)	21%
Overgaard et al, 2024	142	144 – 915 MHz	65 - 70	32% (RT) 50% (RT-HT)	(13%)
b. non-randomised trials / retrospective analyses					
Oldenborg et al., 2015	414	434 MHz	32 (20 – 40)	58%	13%
Lindhorst et al., 2015	248	434 MHz	32	70%	23%
Bakker et al, 2018	262	434 MHz	32	59%	26%
Oldenborg et al, 2019	156	434 MHz	32* 36*	65%	40% 18%
Notter et al., 2020	201	wIRA	20	2-76%**	0.5%

*: comparison of 2 clinics with different dosage in postoperative situation

**: CR according to extensions of recurrences (rClass 0 – IV)

Radiotherapy and the role of hyperthermia in breast cancer
Superficial hyperthermia

technical requirements



«microscopic leasion» «limited leasion» «extended leasion»

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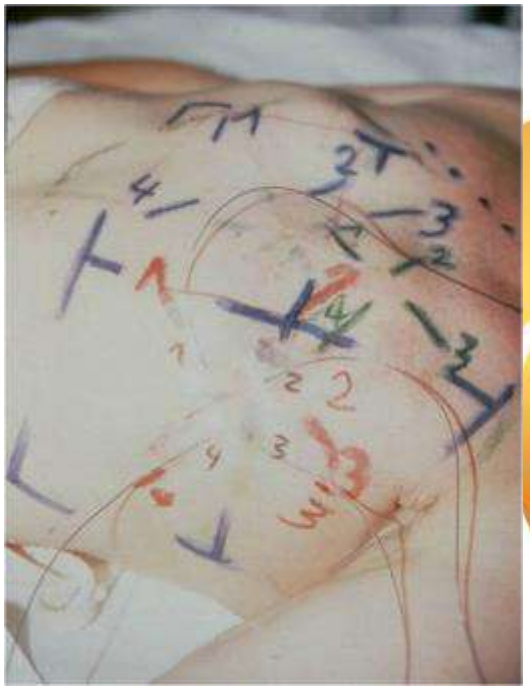
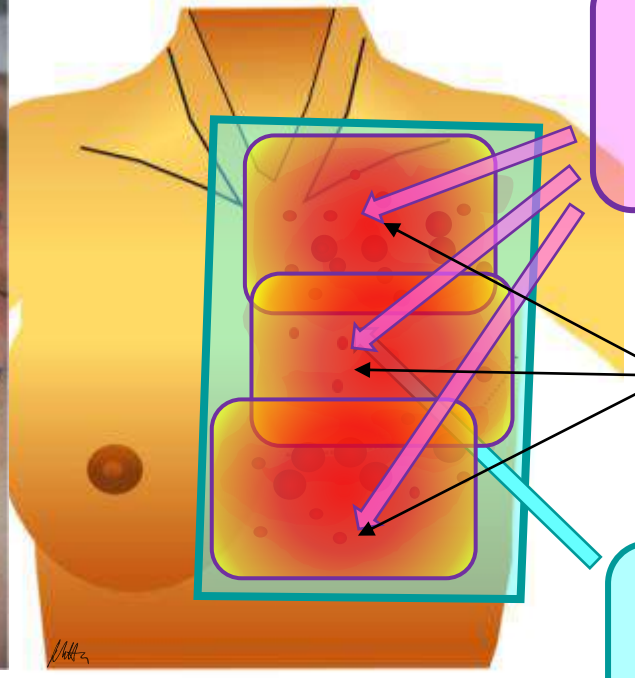
Radiotherapy and the role of hyperthermia in breast cancer
Superficial hyperthermia: how to increase field? „patchwork technique“?



RO KSA 1989 : temperature measurements with thermistors (sensors)



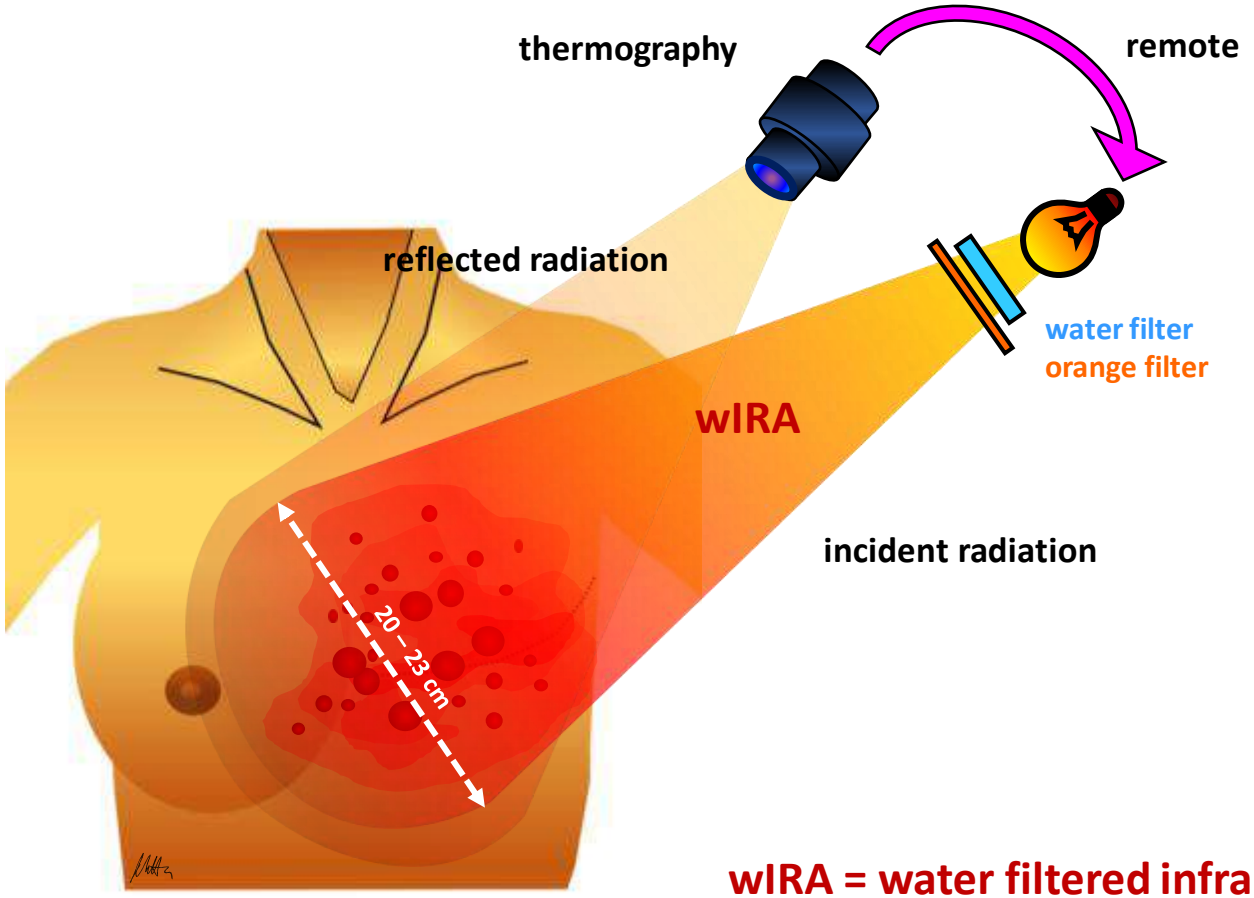
microwave hyperthermia

Temperature control by multiple thermistors for each applicator position !

RT – field
e.g., electrons

KSA 1984 – 2003, CDF 2005 - 2009

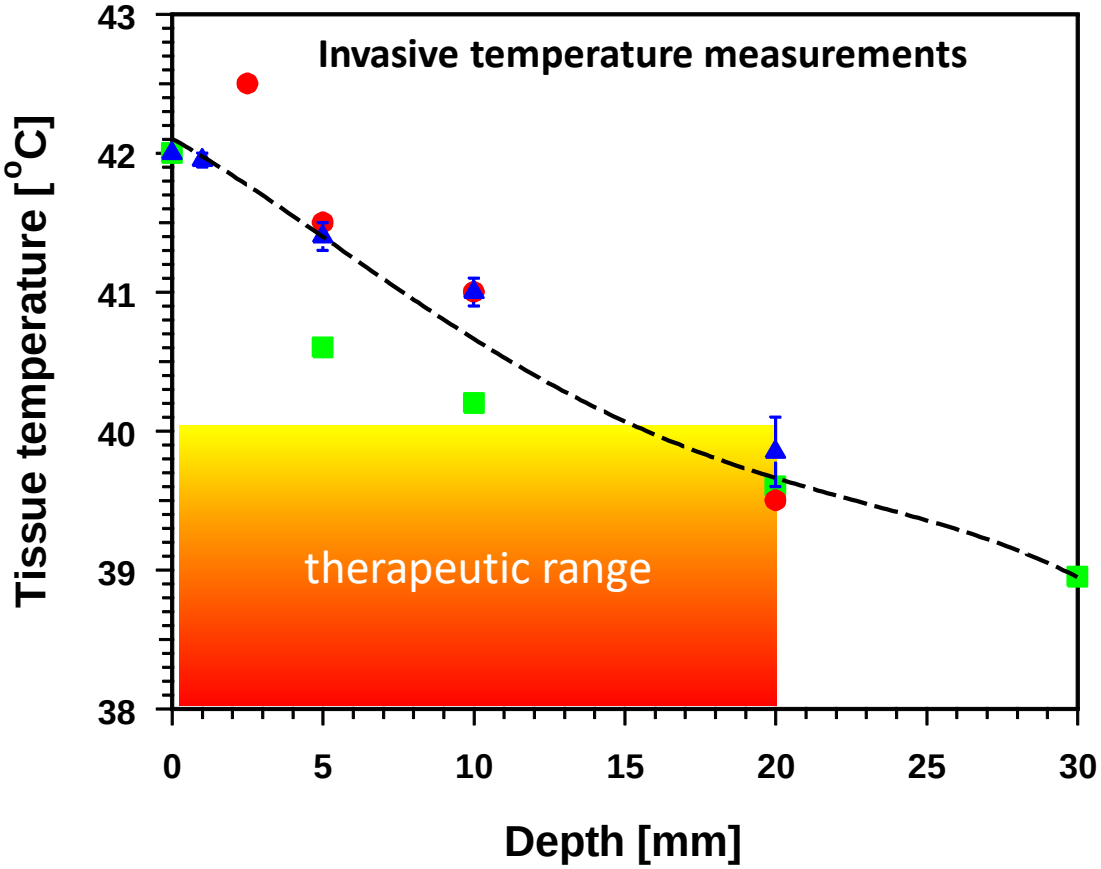
Radiotherapy and the role of hyperthermia in breast cancer
Superficial hyperthermia: how to increase field? Infrared technology?



wIRA = water filtered infrared A

Notter et al, IJH 2016

Radiotherapy and the role of hyperthermia in breast cancer
Thermography-controlled wIRA-hyperthermia

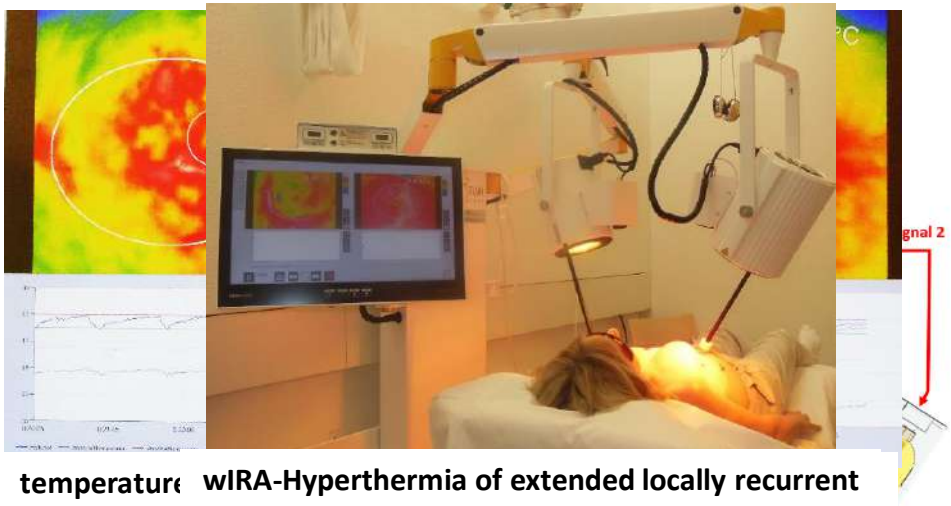


Mean temperature profile during wIRA exposure under steady-state conditions. Measured data in normal tissue (green squares, Hellige et al), tumor tissues (red circles, Seegenschmiedt et al) and recurrent breast cancer (blue triangles, Notter et al).

Notter et al, IJH 2016

Radiotherapy and the role of hyperthermia in breast cancer
Thermography-controlled wIRA-hyperthermia

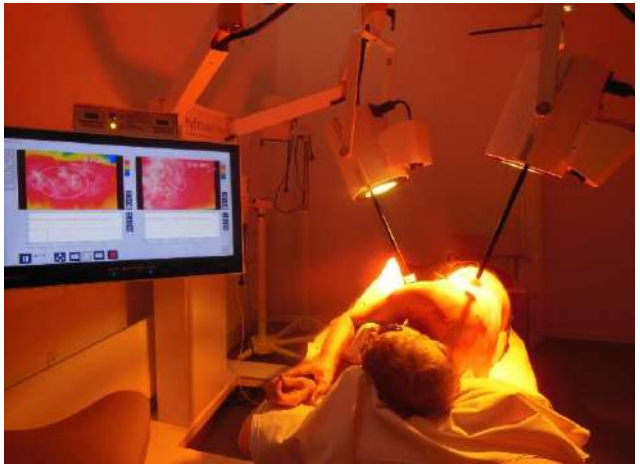
wIRA-Hyperthermia of localized locally recurrent breast cancer: treatment with 1 applicator



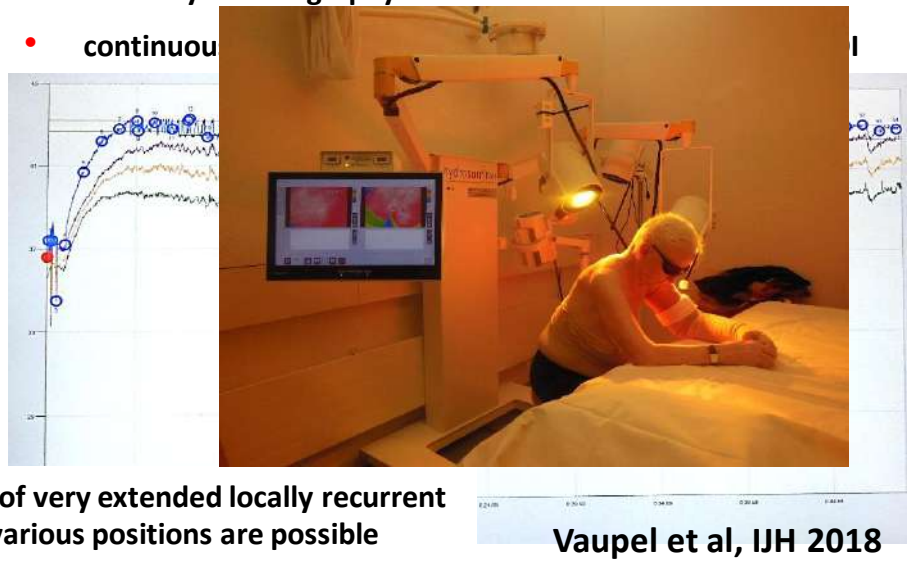
wIRA-Hyperthermia of extended locally recurrent breast cancer

temperature

- visual b
- continuou



wIRA-Hyperthermia of exten
breast can



wIRA-Hyperthermia of very extended locally recurrent breast cancer: various positions are possible

Vaupel et al, IJH 2018

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Radiotherapy and the role of hyperthermia in breast cancer
Timing/sequencing radiotherapy & hyperthermia

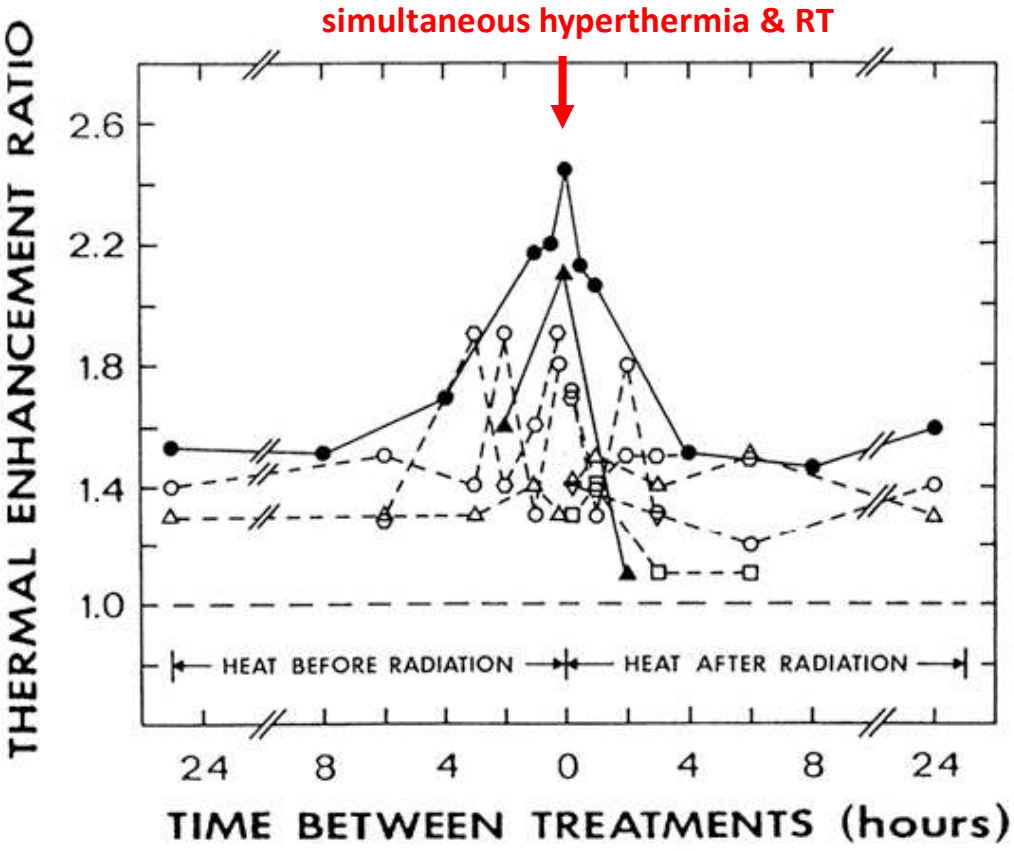

Fig. 2: thermal enhancement ratios (ratio of the radiation doses for radiation alone and radiation plus heat to produce the same effect) for different murine tumour models as a function of the time interval and sequence between heating (42.5 C; 60 min) and irradiation. The results are for mammary carcinomas (C:), carcinoma NT (6), SQ carcinoma (B), sarcomas Fa (B), F (7), and S (,). Figures redrawn from [25,26].

Overgaard 1980, Horsman & Overgaard 1988

Radiotherapy and the role of hyperthermia in breast cancer
Timing/sequencing radiotherapy & hyperthermia

simultaneous hyperthermia & RT KSA since 1986

4.6.1989: cancer en cuirasse before treatment

8.7.1989: 3 weeks after 2 x 4 Gy 43 KV
+ simultaneous hyperthermia 1x/w

Schwegler, Notter 1988

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Radiotherapy and the role of hyperthermia in breast cancer
Timing/sequencing radiotherapy & hyperthermia

- timing is very controversially discussed !
  - different pathways of radiosenzitation !
    - re-oxygenation > 39°C, effect ~ min ?
    - DNA-repair inhibition > 41°C, effect ± 1 (– 3) h ?
    - direct destruction: > 43°C, effect ± 1 h – days ?
    - others ? > 4 h – 2 days ?

  - most frequently used schedule: primary RT, then HT after/within ~1 hour (reason: logistic problems etc.)

  - if only very limited (re)-RT-doses are possible, try to apply as close as possible RT & HT ! (“near simultaneous” approach)

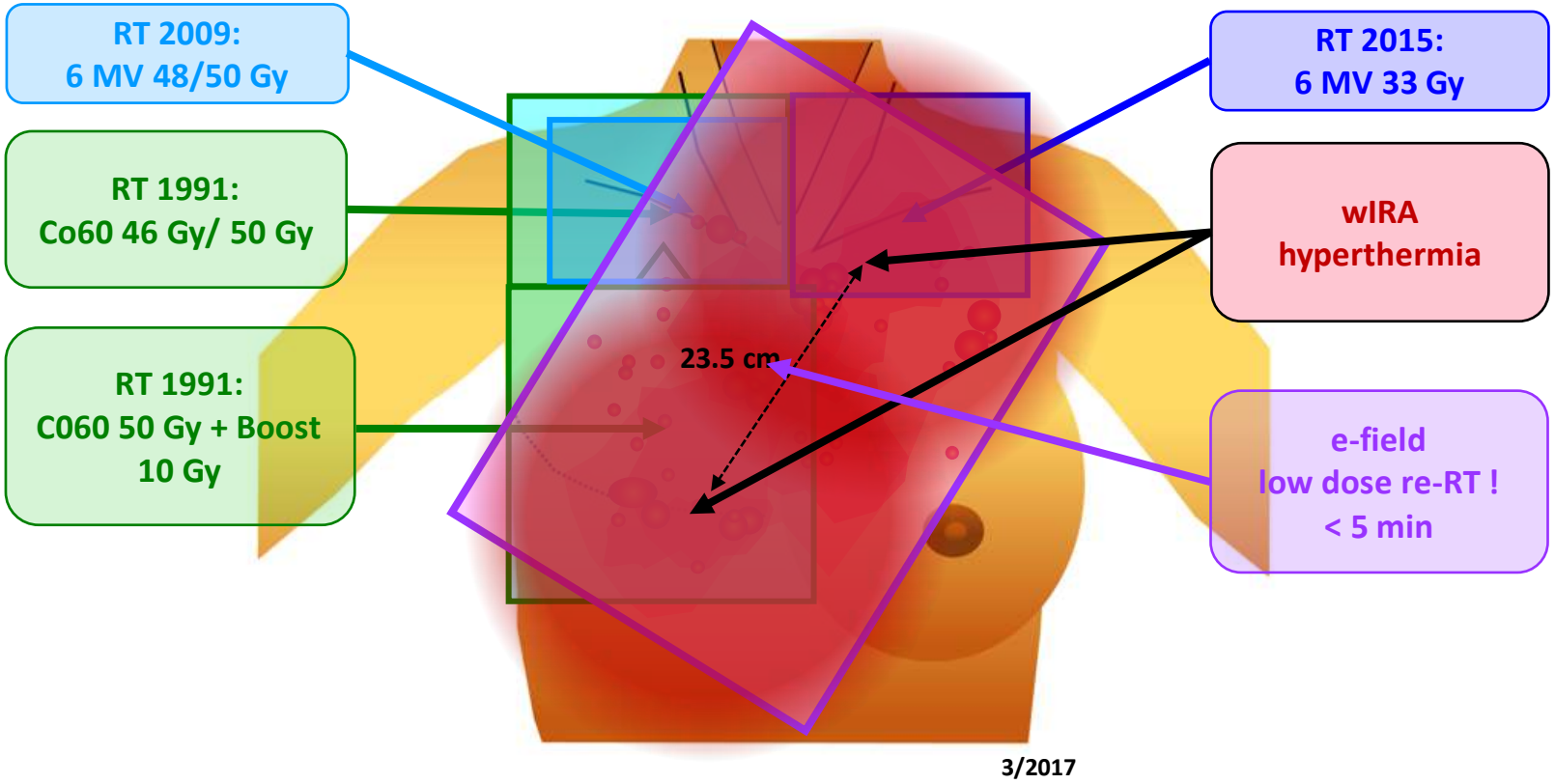
  - to achieve the maximal effect: primary HT and then RT within ~ min, (“Notter-schedule”)

Crezee et al 2019, Kroesen et al 2019, Vaupel et al 2023

Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: purpose

How to re-treat locally ?

former RT and dose (Gy)



Patient B.G, 1941: 1991 BCT for pT1b pN0 M0, locoregional RT Co60, adj. hormone-therapy for 5 years; 2008: 1st local recurrence, mastectomy, hormone-therapy; 2009: PD axilla/supra → re-RT, 1st ChTh; 2010: 2nd local recurrence, 2nd ChTh; 2015: PD lymphnodes, re-RT left supra, 3rd ChTh; 2016: local PD, 4th ChTh; 1/2017: inflammatory recurrence & multiples subcutaneous nodules, 5th ChTh; PD, 3/2017: referral for re-re-RT & hyperthermia

Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: methods (1)

Thermography-guided wIRA-HT :

always before RT
1x/week

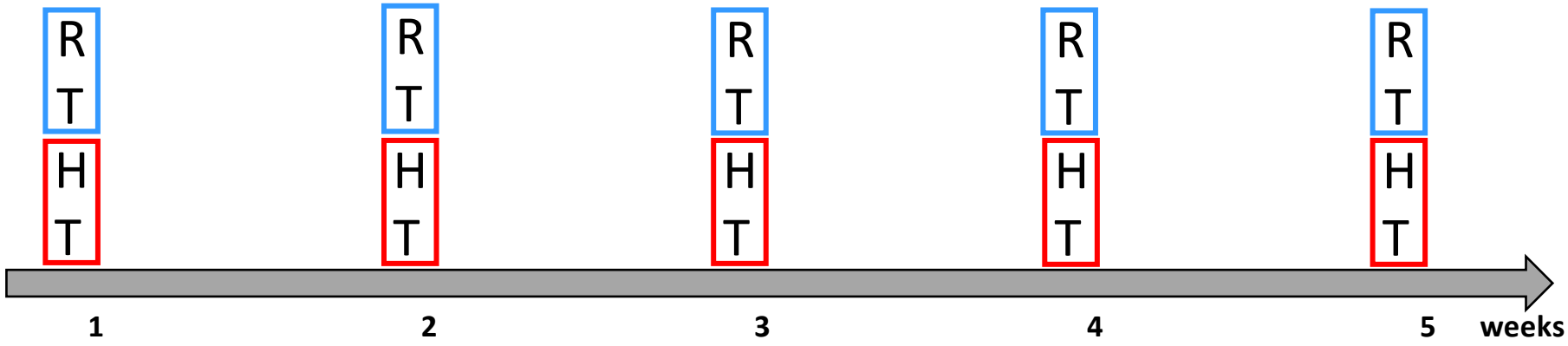
45 – 60 min application
max. tumor surface temperature: 42 – 43°C
max. normal tissue surface temperature: 42 – 43°C

water-filtered infrared A (wIRA), 950 – 1400 nm,
200 mW/cm^2
1 – 2 applicators
Hydrosun TWH 1500® system

Hypofractionated re-RT :

1 – 5 min after termination of HT
1x/week

4 – 12 MeV electrons or photons (VMAT)
SD: 4 Gy
TD 20 Gy
bolus : preheated to 43 – 45°C
transfer to the Linac with thermal shield (blanket)



Notter et al, IJH 2017, 33 (2), 227-236

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Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: methods (2)

- **timing hyperthermia – low dose re-irradiation : the most important !**

1. **after ~45 min hyperthermia : Linac team charges patient data (coordination team Linac – hyperthermia)**
2. **patient is wrapped by a pre-heated blanket and accompagned directly to linac treating room (close to the hyperthermia room! e.g. some meters)**
3. **„speedy“ positioning: with electron fields very fast, with photon fields verification as short as possible/necessary**
4. **application of preheated bolus (45°C) for electron or photon fields**
5. **time end hyperthermia – start RT : ~ 1 ½ min (e-fields)**

Notter et al, IJH 2017, 33 (2), 227-236

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Hyperthermia & re-irradiation in locally recurrent breast cancer proposal of a new classification: simply and reproducible

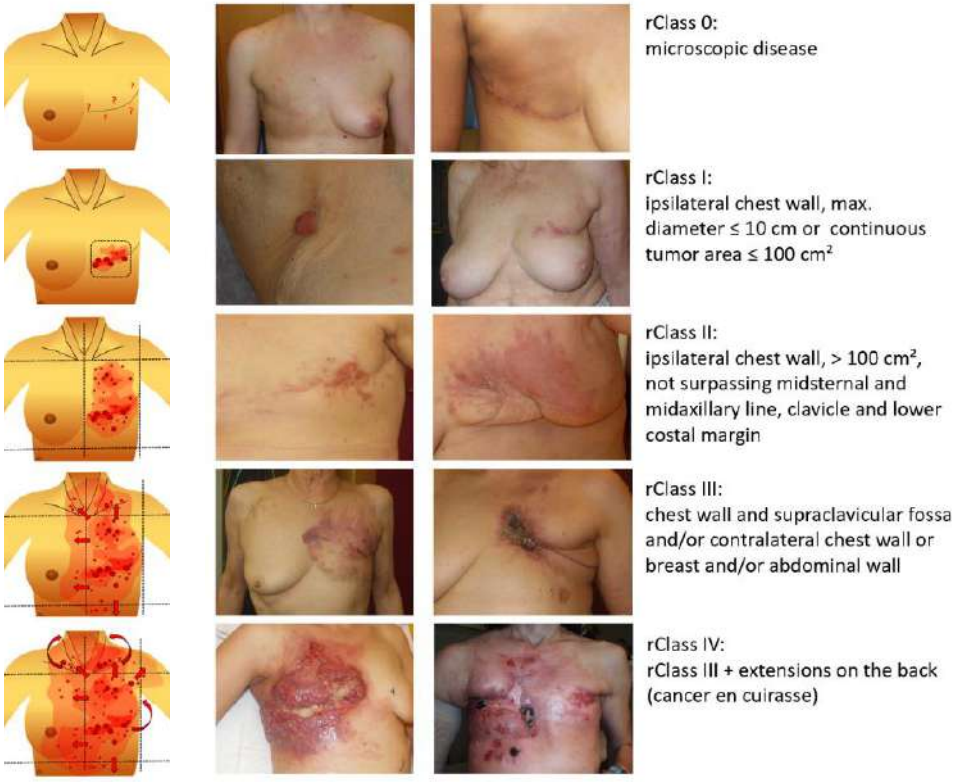
cancers

MDPI

Article

Combined wIRA-Hyperthermia and Hypofractionated Re-Irradiation in the Treatment of Locally Recurrent Breast Cancer: Evaluation of Therapeutic Outcome Based on a Novel Size Classification

Markus Notter [1], Andreas R. Thomsen [2,3], Mirko Nitsche [4], Robert M. Hermann [4], Hendrik A. Wolff [5,6], Gregor Habl [5,7], Karin Münch [1], Anca-L. Grosu [2,3] and Peter Vaupel [2,3,4]



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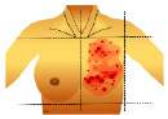
Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: results (1)

Clinical outcome (1): tumor response

	microscopic	macroscopic						
			sizes / classes				other factors	
	class 0 	all	rClass I 	rClass II 	rClass III 	rClass IV 	lymphangiosis	ulceration
n	**31**	**170**	**29**	**56**	**44**	**41**	**115**	**70**
CR		**95%**	22 (**76%**)	34 (**61%**)	16 (**36%**)	1 (**2%**)	41 (**36%**)	12 (**17%**)
PR			7 (**24%**)	30 (**36%**)	27 (**61%**)	34 (**83%**)	68 (**59%**)	52 (**74%**)
NC		6 (**4%**)		2 (**3%**)		4 (**10%**)	4 (**3%**)	4 (**6%**)
PD		3 (**2%**)			1 (**2%**)	2 (**5%**)	2 (**2%**)	2 (**3%**)

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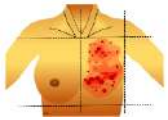
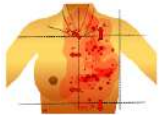
9/2009 – 9/2019 : n = 201 patients with 284 regions
(Notter et al. 2020)

Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: results (2)

Clinical outcome (2): local control & re-recurrences after CR

patients with CR	microscopic	macroscopic						
		all	sizes / classes				other factors	
	rClass 0 		rClass I 	rClass II 	rClass III 	rClass IV 	lymphangiosis	ulceration
n	31	73	22	34	16	1	41	12
LC	68%	67%	77%	62%	69%		59%	58%
Ø LC	6%	29%	9%	38%	31%	100%	41%	42%
LFU	26%	4%	14%					

LC = local control during life time; Ø LC = infield/border re-recurrences after complete response (CR), LFU = lost of follow up

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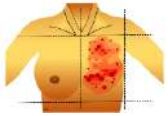
9/2009 – 9/2019 : n = 201 patients with 284 regions
(Notter et al. 2020)

Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: results (3)

Clinical outcome (2): local stabilisation & new local progression after PR

patients with PR	macroscopic						
	all	sizes / classes				other factors	
		rClass I 	rClass II 	rClass III 	rClass IV 	lymphangiosis	ulceration
n	88	7	20	27	34	68	52
LPF	55%	43%	40%	52%	71%	56%	54%
Ø LPF	45%	57%	60%	48%	29%	44%	46%

LPF = locally progression free during life time, Ø LPF = new infield/border progression after partial response (PR)

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9/2009 – 9/2019 : n = 201 patients with 284 regions
(Notter et al. 2020)

Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: side effects

no. of patients evaluated	**201**	**(100%)**
no acute side effects observed	**114**	**(57%)**
acute side effects	**87**	**(43%)**
G1: radiodermatitis grade I	**65**	
scurfs	**10**	
hyperpigmentation	**64**	
G2: radiodermatitis grade II	**4**	
burn with blistering	**1**	
no chronic side effects observed	**145**	**(72%)**
chronic side effects	**56**	**(28%)**
G1: hyperpigmentation	**53**	
G2: new teleangiectasia (moderate)	**7**	

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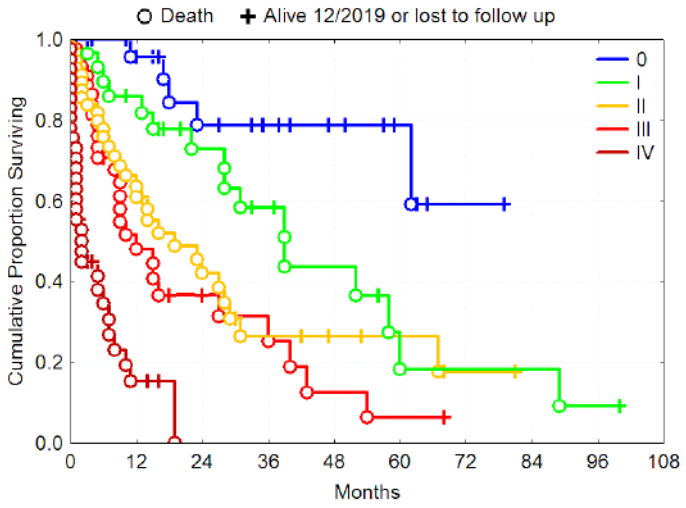
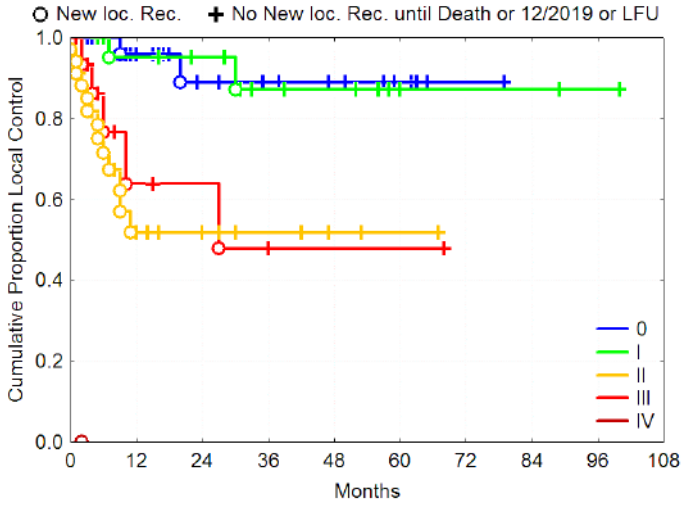
9/2009 – 9/2019 : n = 201 patients with 284 regions
(Notter et al. 2020)

Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: Kaplan-Meier estimates

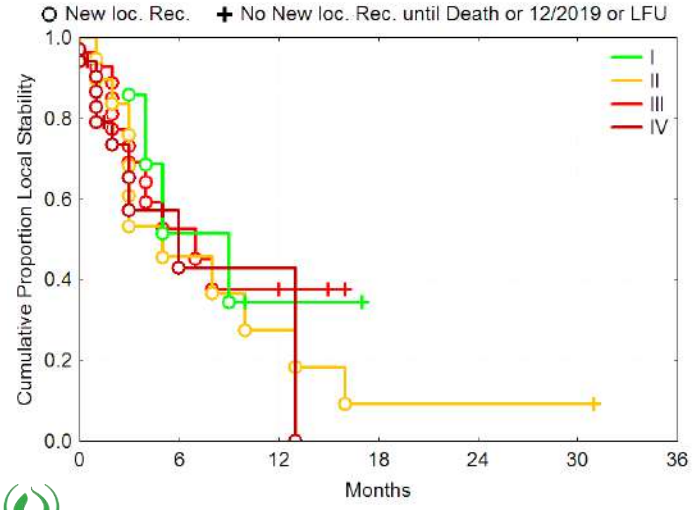
Overall survival stratified by rClasses 0-IV



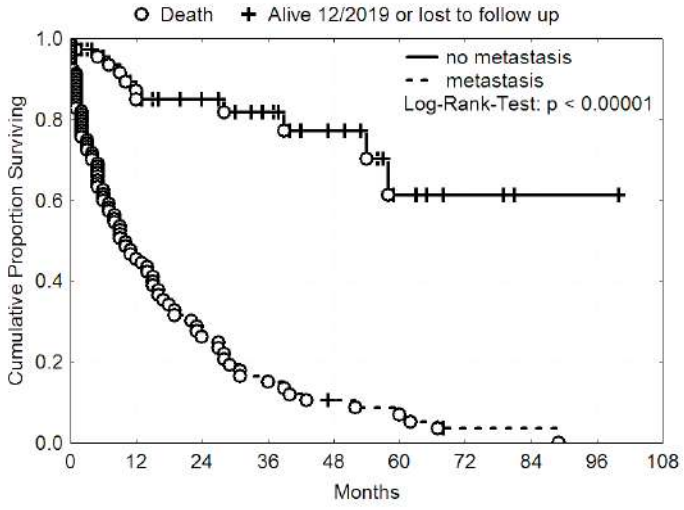
Local Control after CR stratified by rClasses 0-IV



Progression-free interval after PR stratified by rClasses I-IV



Survival and metastatic status at onset of HT/re-RT or thereafter



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9/2009 – 9/2019 : n = 201 patients with 284 regions
(Notter et al. 2020)

Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: summary

Overall response:	**95%**
Reponse in ulcerating tumors:	**91%**
Local control during life time after CR:	**67%**
Local progression free during life time after PR	**54%**
No acute toxicity:	**57%**
Acute toxicity G1-2:	**43%**
No chronic toxcity	**72%**
Chronic toxicity G1-2	**28%**

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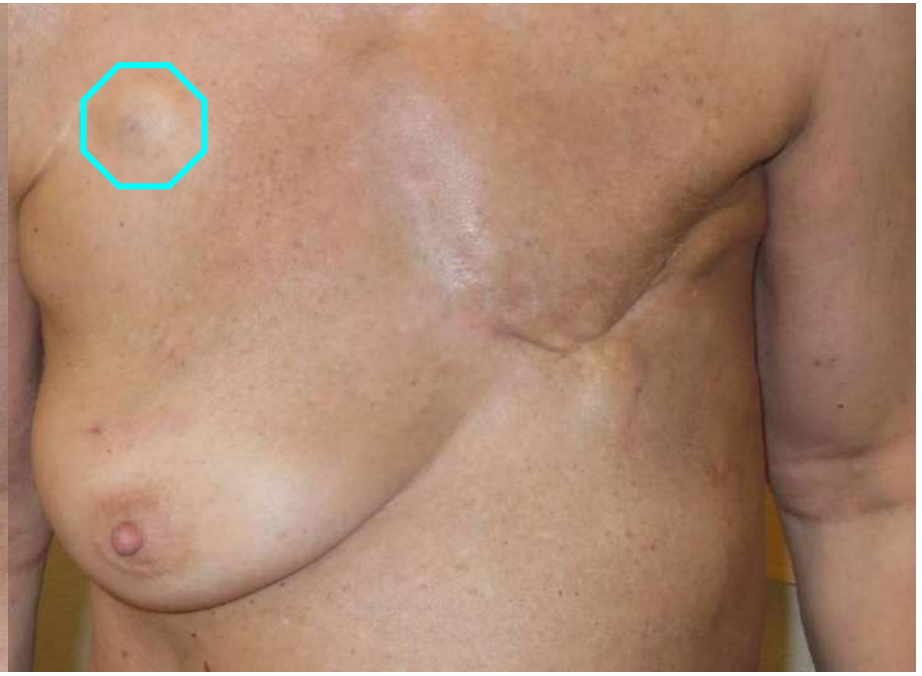
9/2009 – 9/2019 : n = 201 patients with 284 regions
(Notter et al. 2020)

Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: clinical results

PAC = no contraindication for wIRA-hyperthermia!



17.4.2018 : before re-RT & hyperthermia

12.11.2018: after 2 Series with 5 x 4 Gy 1x/w + wIRA-hyperthermia

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Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: clinical results

“cancer en cuirasse” $rClass_{IV}$

10.7.2018 : before re-RT & hyperthermia

12.11.2018 : 2 mts after 5 x 4 Gy + wIRA-HT

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Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: clinical results

“cancer en cuirasse” $rClass_{IV}$

extended recurrent breast cancer : former RT-dose both chest walls: 54 Gy 9.9.2014 1st consultation

9.1.2015 : 6 weeks after 5 x 4 Gy + wIRA 1x/w

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Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: clinical results

“cancer en cuirasse” $rClass_{IV}$

21.12.2017 : before treatment

30.4.2018 : 9 weeks after 5 x 4 Gy + HT

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Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: care expenses

“cancer en cuirasse” $rClass_{IV}$

- daily expenditure of time !
- special bandages ?
- superinfection ?
- decaying tumor – odor etc. ?
- special shower head ?

- how can I go outside ?
- who helps at home ?
- economic impacts ?
- quality of life ?
- psychological situation ?
- social contacts ?
- isolation ?
- how do I dress ?
- can I eat by myself / cook ?
- how independent can I stay ?

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Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: QoL-analysis (1)

Need of wound care or bandages		
before onset of sHT&re-RT	70	100%
after sHT&re-RT		
Ø bandages etc.	41	59%
reduced	24	34%
equal	3	4%
increased	2	3%

Σ 93%

Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: QoL-analysis (2)

“cancer en cuirasse” $rClass_{IV}$

distinct reduction of wound care or bandages !

17.10.2017 : before re-RT & hyperthermia

12.6.2018: follow up

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Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: QoL-analysis (3)

Need of analgetics		
before onset of sHT&re-RT	25	100%
after sHT&re-RT		
Ø analgetics	7	28%
reduced	13	52%
equal	4	16%
increased	1	4%
new pain*	1/45	2%

Σ 80%

*: 1 patient had new pain and need of analgetics

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Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: clinical results

hemangiosarcoma after BCT

11.1.2018 (4th recurrence)

1.10.2019: 20 mts after 5 x 4 Gy + wIRA-HT (4th series)

Radiotherapy and the role of hyperthermia in breast cancer
wIRA-hyperthermia & low dose re-irradiation: clinical results

hemangiosarcoma after BCT

23.4.2019 : preoperative situation

11.4.2023 : follow up: 4 years after re-RT with 5 x 4 Gy 1x/w + wIRA-HT

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Radiotherapy and the role of hyperthermia in breast cancer conclusions (1)

- (wIRA)-hyperthermia and low dose re-irradiation is a very effective palliation method
  - high remission rates obtained
  - these remissions can be maintained for life time (>50%)
  - out patient basis
  - very low toxicity
  - improves life quality very effectively
  - can be even repeated in re-recurrences

- extreme low dose re-RT :
  - timing hyperthermia & re-RT crucial !
  - not inferior compared to results from higher re-RT-doses & MW-HT

Radiotherapy and the role of hyperthermia in breast cancer conclusions (2)

- There is definitively a huge potential to help patients with a relatively well tolerated, effective and easy way, in addition with rather low economic implications compared to other cancer care!
  - Locally recurrent breast cancer (LRBC)
  - Locally advanced breast cancer
  - Radiation associated angiosarcoma of the breast (RAASB)

- → as already established in Switzerland, superficial hyperthermia and re-irradiation should be accepted as a standard in specific situations