1. Scopo

Lo scopo della presente relazione è quello di valutare se esistono dati clinici sufficienti a supportare per i dispositivi HY-DEEP 600, dispositivi medici per la terapia oncologica ipertermica prodotti e commercializzati da Andromedic Srl (di seguito anche il/i "Prodotto/i"):

- La conformità ai relativi Requisiti Generali di Sicurezza e Prestazione stabiliti dal Regolamento Europeo sui Dispositivi Medici (EU MDR 2017-745).
- Un profilo rischio-beneficio favorevole, in relazione all'uso previsto/alle indicazioni d'uso e alla popolazione target, come indicato nell'etichettatura
- La valutazione della necessità di condurre studi di follow-up clinico post-market (PMCF).

La presente relazione di valutazione clinica è redatta secondo i metodi riportati nel piano di valutazione clinica dei prodotti (vedere Appendice 1 - Piano di valutazione clinica).

2. Contesto

2.1. Aspetti normativi e di conformità

La conformità al regolamento sui dispositivi medici (MDR) richiede che il fabbricante di dispositivi medici dimostri che la sicurezza e le prestazioni dichiarate dei suoi prodotti sono raggiunte in condizioni d'uso normali. In genere, per dimostrare la conformità ad alcuni Requisiti Generali di Sicurezza e Prestazioni, sono necessari dati clinici ottenuti direttamente da studi clinici condotti con il/i Prodotto/i in questione, oppure una valutazione critica dei dati (pubblicati e/o non pubblicati) generati dall'esperienza clinica con dispositivi e/o tecnologie equivalenti (o simili).

Questa relazione ha lo scopo di fornire evidenze cliniche e scientifiche a sostegno della dimostrazione della sicurezza e delle prestazioni dei Prodotti secondo le indicazioni riportate nell'Allegato XIV della MDR in relazione all'uso previsto e alla popolazione target; inoltre, fornisce le evidenze cliniche di base per stabilire se il profilo rischio-beneficio (come riassunto nel file di analisi del rischio del Prodotto) debba essere rivalutato, determinando così l'eventuale necessità di condurre studi clinici di follow-up con i Prodotti già in commercio (ossia, studi di follow-up clinico post-market - PMCF), come previsto dalla Parte B dell'Allegato XIV della MDR. Gli studi PMCF garantiscono la verifica della sicurezza e delle prestazioni a lungo termine nella fase post-marketing quando la valutazione dei dati clinici pre-market o il loro monitoraggio continuo nella fase post-market lasciano (o generano) questioni cliniche irrisolte o modificano il profilo rischio-beneficio dei prodotti a un livello inaccettabile.

Questo rapporto comprende una ricerca online di dati clinici pubblicati su riviste scientifiche relativi all'uso delle radiofrequenze per l'oncologia ipertermica, in linea con l'uso principale previsto per i Prodotti, e una ricerca online di altri dati di sicurezza clinica relativi ai Prodotti (eventi avversi, incidenti e malfunzionamenti) raccolti nell'ambito delle attività di sorveglianza post-market del Fabbricante, compresi quelli relativi a dispositivi simili. Vengono presi in considerazione anche eventuali studi PMCF già pianificati prima della stesura della presente valutazione clinica.

I seguenti documenti sono applicabili alla presente valutazione clinica:

- Regolamenti
o Regolamento europeo sui dispositivi medici (EU MDR 2017/745)
- Norme
o EN 60601-1-6:2010/A1:2015: Usabilità
o EN ISO 10993-1:2021: Valutazione biologica dei dispositivi medici

o EN ISO 14971:2019: Applicazione della gestione del rischio ai dispositivi medici.

- Linee guida
o Valutazione clinica GHTF SG5-N2R8:2007 (maggio 2007). Sito web: www.imdrf.org/

o Lawrence R, U.S. Preventive Services Task Force Edition (1989). Guida ai servizi clinici di prevenzione - Appendice A.
o MDCG 2020-5 - Valutazione clinica - Equivalenza - Guida per i produttori e gli organismi notificati - Procedure cliniche.
o MDCG 2020-7 - Modello di piano di follow-up clinico post-market (PMCF) - Guida per i produttori e gli organismi notificati.

- Procedure cliniche
o Piano di valutazione clinica: vedi Appendice 1 - Piano di valutazione clinica
o Protocollo di valutazione clinica: vedere sezione 5
o Piano di follow-up clinico post-commercializzazione (vedi piano PMS Piano di sorveglianza post-commercializzazione: inserire link)

2.2. Requisiti essenziali dei prodotti che richiedono il supporto di dati clinici e scientifici
Andromedic Srl ha identificato i seguenti Requisiti Generali di Sicurezza e Prestazione (sezione FT All. 01 RES) che necessitano di un supporto da parte dei dati clinici e scientifici raccolti e valutati in questa relazione:

- GSPR 1: I dispositivi devono raggiungere le prestazioni previste dal fabbricante e devono essere progettati e fabbricati in modo tale che, nelle normali condizioni d'uso, siano adatti allo scopo per cui sono stati progettati. Devono essere sicuri ed efficaci e non devono compromettere le condizioni cliniche o la sicurezza dei pazienti, né la sicurezza e la salute degli utilizzatori o, se del caso, di altre persone, a condizione che gli eventuali rischi associati al loro uso costituiscano rischi accettabili se valutati rispetto ai benefici per il paziente e siano compatibili con un elevato livello di protezione della salute e della sicurezza, tenendo conto dello stato dell'arte generalmente riconosciuto.
- GSPR 6: Le caratteristiche e le prestazioni di un dispositivo non devono essere influenzate negativamente in misura tale da compromettere la salute o la sicurezza del paziente o dell'utilizzatore e, se del caso, di altre persone durante la vita del dispositivo, come indicato dal fabbricante, quando il dispositivo è sottoposto alle sollecitazioni che possono verificarsi nelle normali condizioni d'uso ed è stato sottoposto a una corretta manutenzione in conformità alle istruzioni del fabbricante.
- GSPR 8: Tutti i rischi noti e prevedibili e gli eventuali effetti collaterali indesiderati devono essere ridotti al minimo ed essere accettabili se confrontati con i benefici valutati per il paziente e/o l'utilizzatore derivanti dalle prestazioni ottenute dal dispositivo in condizioni d'uso normali.

- GSPR 23.1(g): Ogni dispositivo deve essere accompagnato dalle informazioni necessarie per identificare il dispositivo e il suo fabbricante, nonché da tutte le informazioni sulla sicurezza e sulle prestazioni rilevanti per l'utilizzatore o per qualsiasi altra persona, a seconda dei casi. Tali informazioni possono figurare sul dispositivo stesso, sull'imballaggio o nelle istruzioni per l'uso e, se il fabbricante dispone di un sito web, devono essere rese disponibili e aggiornate su tale sito, tenendo conto di quanto segue: [...] I rischi residui che devono essere comunicati all'utilizzatore e/o ad altre persone devono essere inclusi come limitazioni, controindicazioni, precauzioni o avvertenze nelle informazioni fornite dal fabbricante.

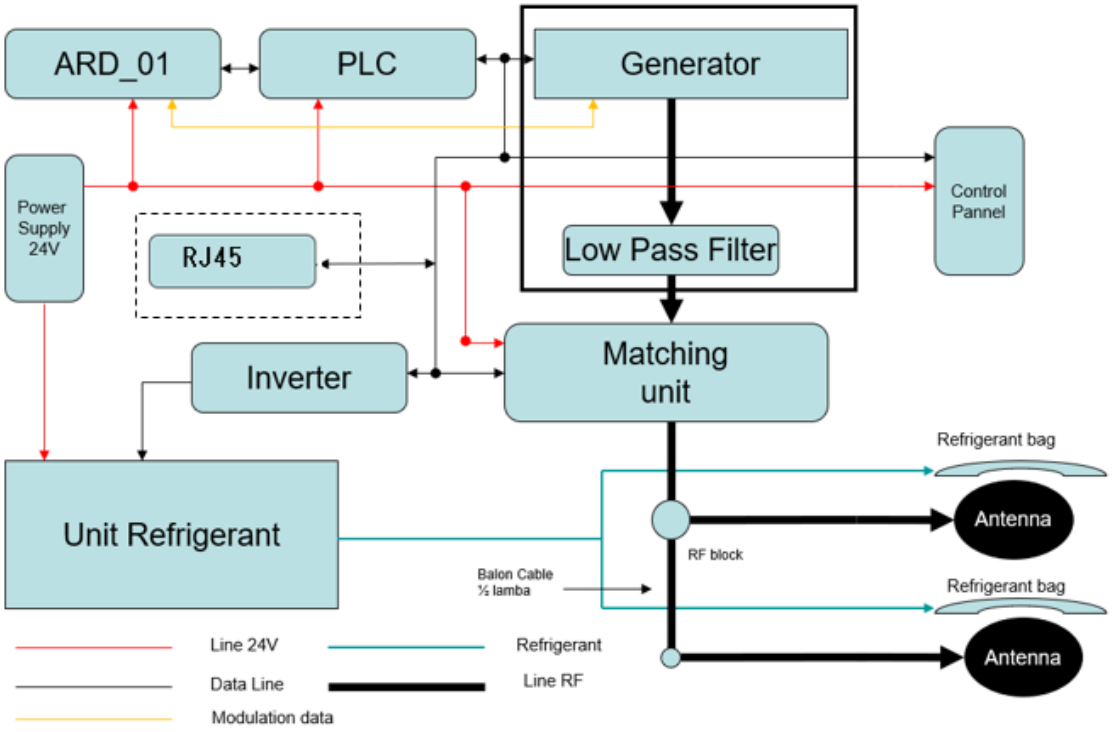
3. Dettagli generali
3.1 Informazioni sul prodotto
Nome attuale del prodotto HY-DEEP 600 WM
Codice prodotto attuale HY-DEEP
Classificazione IIB
Produttore legale Andromedic srl, via Casale di Malatesta, 10 - 00049 Velletri (Rm)

3.2 Descrizione del prodotto
Il dispositivo medico oggetto della presente documentazione tecnica denominato HY-DEEP 600WM, è un apparecchio per il trattamento di Patologie Oncologiche Solide Primarie o Secondarie (metastasi) dotato di ruote per essere facilmente spostato, equipaggiato con un pannello Touch da 12" per la gestione completa dell'apparecchio, fornito di antenne circolari refrigerate che vanno direttamente sul paziente per l'emissione di radiofrequenza a scopo terapeutico in campo oncologico.

L'HY-DEEP 600WM è costituito da un generatore di radiofrequenza a 13,56 MHz con una potenza massima di 600 watt pulsati in modalità OOK (on off key) con accoppiamento capacitivo, ed è fornito con due set di antenne che hanno identiche caratteristiche costruttive e prestazionali, differenziandosi solo per le dimensioni geometriche che consentono un migliore adattamento in funzione del distretto anatomico da trattare.
La destinazione d'uso è definita come segue: "Apparecchiatura per il trattamento delle Patologie Oncologiche mediante l'innalzamento della temperatura loco regionale per mezzo di un generatore di Radiofrequenza ad accoppiamento capacitivo."
L'HY-DEEP 600WM deve essere utilizzato solo da personale medico qualificato, come medici e infermieri, che siano stati precedentemente formati e addestrati dal produttore o da un rivenditore autorizzato.
Il dispositivo medico è destinato a pazienti con indicazioni al trattamento e privi di controindicazioni all'ipertermia, come indicato nella sezione 2.2 del manuale d'uso.

3.3 Livello di evidenza clinica per dimostrare la conformità all'SPGR
I Prodotti sono dispositivi medici per il trattamento del cancro mediante ipertermia destinati a essere utilizzati nei bambini e nei soggetti adulti come terapia aggiuntiva a quelle convenzionali. I Prodotti incorporano un software che consente all'utente di controllare il dispositivo medico, inserire i dati demografici del paziente, impostare la potenza di uscita, selezionare protocolli di trattamento predefiniti.
Le specifiche tecniche dei Prodotti riportate nella sezione 3.2 sono state accuratamente verificate per raggiungere l'uso previsto (vedere sezione 3.6).

Ai sensi dell'articolo 61 dell'MDR UE 2017/745, il Fabbricante ha riconosciuto che l'uso previsto dei Prodotti (sezione 3.6) è raggiunto dalla combinazione dei seguenti componenti minimi:



Dopo aver preso in considerazione il fascicolo di analisi dei rischi dei Prodotti (sezione FT All. 02 Gestione dei Rischi), il Fabbricante riconosce inoltre che la generazione di calore mediante principio di radiofrequenza comporta il profilo beneficio-rischio meno favorevole nei Prodotti. Pertanto, ai fini della presente relazione di valutazione clinica, il livello di evidenza clinica per dimostrare la conformità ai requisiti generali di sicurezza e prestazione dell'UE di cui al paragrafo 2.2 è stato determinato sulla base di dati clinici di alta qualità relativi ai benefici, ai rischi e alla sicurezza dell'uso della radiofrequenza per la generazione locale di calore nei tessuti (ipertermia) come coadiuvante della terapia antitumorale (come meglio specificato nel paragrafo 4), quando i Prodotti sono utilizzati in condizioni d'uso normali e per lo scopo previsto riportato nel paragrafo 3.6.
Ulteriori dettagli sul piano di valutazione clinica dei Prodotti oggetto della presente relazione di valutazione clinica sono riportati nell'Appendice 1 - Piano di valutazione clinica.

3.4 Materiali e composizione chimica
I Prodotti sono realizzati con materiali diversi, il Dispositivo Medico NON comporta materiali a contatto diretto o indiretto con il paziente, come indicato nella gestione del rischio, è sempre previsto un materiale di separazione tra le antenne e la pelle (vedi Allegato 2 Gestione del rischio - Allegato 5 IFU > Manuale HYDEEP).
Sulla base di tale documento, Andromedic Srl conclude che i Prodotti oggetto del presente studio clinico
3.5 Sterilità
I Prodotti e i loro accessori non sono sterili e non vengono forniti sterili.

3.6 Destinazione d'uso
3.6.1 Indicazioni d'uso
Il suo utilizzo è destinato al trattamento di patologie neoplastiche e/o correlate: escluso il trattamento di patologie del sistema nervoso o cardiovascolare, è possibile trattare tutti i distretti anatomici grazie alla possibilità di cambiare le antenne fornite come accessori, adattandone le dimensioni al distretto anatomico da trattare.

3.6.2 Pazienti target e popolazione di utenti

Popolazione di pazienti prevista
I prodotti sono destinati all'uso in età pediatrica e adulta, a partire dai 14 anni di età.

Popolazione di utilizzatori prevista
Il Prodotto deve essere utilizzato da personale autorizzato, adeguatamente qualificato, esperto e addestrato all'uso della terapia antitumorale ipertermica. Il dispositivo non è destinato all'uso da parte di un profano.

3.6.3 Controindicazioni e precauzioni
Come riportato nel manuale d'uso dei Prodotti e nella descrizione tecnica contenuta nella scheda tecnica, si applicano le seguenti controindicazioni:

- Si veda la sezione 00 Introduzione, punto 1.1c.

Tali controindicazioni derivano dalle attuali conoscenze e dallo stato dell'arte sui potenziali rischi derivanti dall'uso della radiofrequenza per la generazione di calore nei tessuti umani. Tali controindicazioni confermano le conclusioni riportate nella sezione 3.3 in merito all'obiettivo principale di questa relazione di valutazione clinica e al livello di evidenza clinica richiesto per supportare la dimostrazione di conformità dei Prodotti ai requisiti generali di sicurezza e prestazione dell'UE.

4. Contesto clinico e stato dell'arte

4.1. Breve riassunto della terapia antitumorale ipertermica
- Vedere sezione 00 Introduzione punto 1.1d

4.2. Sintesi di altre tecniche mediche per la terapia del cancro
La radioterapia è un tipo di radiazione ionizzante (ad alta energia) che distrugge le cellule tumorali nell'area trattata danneggiando il DNA di queste cellule. Le radiazioni colpiscono anche le cellule normali. Ciò può causare effetti collaterali nell'area trattata. Di solito gli effetti collaterali migliorano alcune settimane dopo il trattamento.
trattamento, ma alcuni potrebbero continuare a lungo termine. La radioterapia può essere utilizzata per cercare di curare il cancro, per ridurre la possibilità che si ripresenti o per aiutare ad alleviare i sintomi. Quasi 50 persone su 100 (50%) sono sottoposte a radioterapia durante il trattamento del cancro. La maggior parte dei tipi di radioterapia utilizza fotoni. Ma potrebbero essere utilizzati anche elettroni o, più raramente, protoni. L'obiettivo è quello di somministrare una dose elevata di radiazioni al tumore, ma una dose quanto più bassa possibile alle cellule sane circostanti. In questo modo si ottiene la massima possibilità di curare o ridurre il tumore, riducendo al contempo il rischio di effetti collaterali. La maggior parte delle persone viene sottoposta a un trattamento quotidiano dal lunedì al venerdì, con un periodo di riposo nel fine settimana. Ma questo può variare. La radioterapia può essere facilmente combinata con l'ipertermia (radiazioni non ionizzanti), mediante la somministrazione di una-due sedute alla settimana durante il ciclo di irradiazione, con l'obiettivo di aumentare il tasso di uccisione delle cellule tumorali, essendo l'ipertermia priva di effetti collaterali sulle cellule sane. Dal punto di vista biologico, l'ipertermia ha due diversi tipi di interazioni con le radiazioni. In primo luogo, il calore ha un effetto radiosensibilizzante. Questo effetto è più evidente con l'applicazione simultanea, ma è della stessa entità sia nel tumore che nel tessuto normale e non migliorerà il rapporto terapeutico a meno che il

tumore non sia riscaldato a una temperatura più elevata rispetto al tessuto normale. In secondo luogo, l'ipertermia ha un effetto citotossico diretto e un trattamento termico moderato da solo può distruggere quasi selettivamente le cellule tumorali in un ambiente cronicamente ipossico e acido, privo di nutrimento. Poiché queste cellule sono le più radioresistenti, è necessaria una dose minore di radiazioni per controllare le restanti cellule più radiosensibili. Se si riscaldano anche i tessuti normali critici irradiati, la citotossicità viene sfruttata al meglio se il calore viene somministrato almeno 3-4 ore dopo l'irradiazione. L'entità dell'effetto sensibilizzante e citotossico dipende dalla temperatura e dal tempo di riscaldamento. Clinicamente, il riscaldamento di tumori superficiali (ad esempio, mammella, linfonodi del collo e melanoma maligno) ha confermato il razionale biologico dell'uso dell'ipertermia come coadiuvante della radioterapia. Una panoramica dei dati disponibili fornisce rapporti di potenziamento termico di circa 1,5 in diversi siti tumorali superficiali dopo il riscaldamento esterno. Questo è l'effettivo beneficio aggiunto dall'ipertermia alla radioterapia.

4.3. Prodotti simili ed equivalenti

I prodotti oggetto del presente rapporto di valutazione clinica sono identici (e quindi equivalenti) a quelli già immessi sul mercato secondo la precedente Direttiva UE 93/42. La tabella di equivalenza riportata di seguito è redatta secondo la MDCG 2020-5.
Non sono state apportate modifiche significative alla progettazione o alla fabbricazione dei Prodotti tra la loro ultima immissione sul mercato ai sensi della Direttiva MDD (dispositivi legacy) e la versione attuale sottoposta alla prima certificazione ai sensi del Regolamento MDR.
Inoltre, ai fini della valutazione dei dati di vigilanza provenienti dai database online (cioè malfunzionamenti ed eventi avversi, paragrafo 5.5), nel piano PMS è riportata una dimostrazione di somiglianza con altri dispositivi medici destinati a essere utilizzati per il riscaldamento dei tessuti tumorali.

5. Protocollo di valutazione clinica

5.1. Premessa

I Prodotti fabbricati da Andromedic Srl sono commercializzati da oltre 10 anni.
L'archivio del produttore comprende dati preclinici e rilevanti per le diverse applicazioni per le quali i prodotti sono destinati a essere utilizzati.

Sulla base del piano di valutazione clinica (si veda l'Appendice 1 - Piano di valutazione clinica (redatto in conformità alla Parte A - Allegato XIV della MDR dell'UE), la presente relazione:

- comprende una ricerca e una valutazione dei dati già in possesso del Fabbricante
- Include una ricerca nelle principali banche dati cliniche e scientifiche di pubblicazioni scientifiche di alto livello di evidenza e/o norme tecniche e/o dichiarazioni ufficiali con il livello di evidenza clinica discusso nella sezione 3.3 e finalizzato a supportare la dimostrazione di conformità all'SPGR riportata nella sezione 2.2.
- Nell'ambito delle attività di PMS in atto, è prevista una ricerca nei principali siti di segnalazione di eventi avversi/malfunzionamenti per dispositivi medici con destinazione d'uso/codice prodotto simili, tenendo conto anche dell'equivalenza e della somiglianza con i Prodotti oggetto della presente relazione, come indicato nella sezione 4.3, per una più approfondita caratterizzazione e comprensione dei rischi e delle controindicazioni noti, nonché per l'identificazione di potenziali nuovi rischi e/o controindicazioni che richiederebbero la conduzione di studi PMCF con i Prodotti.
- Nell'ambito delle attività di PMS in corso, è compresa l'analisi dei dati di PMS derivati dai prodotti equivalenti precedentemente approvati con MDD, al fine di sostenere le conclusioni sulla necessità di condurre studi PMCF con i Prodotti.

5.2. Sintesi del protocollo di ricerca della letteratura

- Periodo in cui è stata condotta la ricerca clinica: Agosto 2022
- Ricerca clinica condotta da: Prof. Sergio Maluta
- Criteri di equivalenza del prodotto: paragrafo 4.3

- Strategia per la ricerca clinica, scientifica e sugli eventi avversi: paragrafi 5.3 e 5.4
- Strategia per la valutazione dei dati clinici: paragrafo 5.7.

5.3. Criteri predefiniti per la selezione di articoli scientifici da banche dati online

5.3.1. Criteri di inclusione

I seguenti criteri generali per l'inclusione degli articoli scientifici sono stati utilizzati per valutare l'appropriatezza degli articoli estratti dalle banche dati online e, di conseguenza, la loro analisi nell'ambito della presente valutazione clinica:

a) L'articolo contiene revisioni o revisioni sistematiche, con o senza meta-analisi.
b) L'articolo/lo studio clinico non contiene informazioni sufficienti sulla sicurezza/prestazioni dei prodotti oggetto della presente valutazione clinica (ad es. studi clinici con disegno o esiti diversi dall'ambito della presente relazione, o articoli con metodologia di bassa qualità o con elevato rischio di bias) ma contiene dettagli importanti per una valutazione complessiva della sicurezza della tecnologia utilizzata nei prodotti.
c) Articoli pubblicati negli ultimi 10 anni o prima, nel caso in cui riportino dettagli tecnici importanti o nel caso di studi "milestone".

Results

Summary of the data to be analyzed

Clinical, scientific, vigilance and post-market data were collected and further selected before appraisal, using the methods indicated in section **Errore. L'origine riferimento non è stata trovata.**.

From the Reviews and Systematic Reviews obtained in Pubmed (n =39 , see **Errore. L'origine riferimento non è stata trovata.**), 32 satisfied the additional inclusion criteria set forth in section **Errore. L'origine riferimento non è stata trovata.** and were therefore selected for further appraisal.

Three clinical publications part of the Manufactuer’s archive and fulfilling the inclusion and exclusion criteria set forth in section **Errore. L'origine riferimento non è stata trovata.** were added to the results (section **Errore. L'origine riferimento non è stata trovata.**), together with the Products’ user manual, risk analysis document and an extract of the Products’ post-market surveillance data (sections **Errore. L'origine riferimento non è stata trovata.**, **Errore. L'origine riferimento non è stata trovata.** and **Errore. L'origine riferimento non è stata trovata.**).

All the results obtained in the US MAUDE (n = 0) and in the Italian Ministry of Health database were selected for further appraisal (section **Errore. L'origine riferimento non è stata trovata.**).

Clinical and scientific literature appraisal

Summary of literature to be appraised

The online search in Pubmed using the search string defined in section **Errore. L'origine riferimento non è stata trovata.** and filtered using the inclusion and exclusion criteria defined in section **Errore. L'origine riferimento non è stata trovata.** is reported in **Errore. L'origine riferimento non è stata trovata.**.

From a total 39 results, the ones reported in the following table (no. = 32) were selected for further appraisal.

Title	Authors	Journal/Book	Publication Year
Randomized trial of hyperthermia and radiation for superficial tumors.	Jones EL, Oleson JR, Prosnitz LR,	J Clin Oncol. 2005;23:3079–3085.	2005

Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials—International Collaborative Hyperthermia Group.	Vernon CC, Hand JW, Field SB,	Int J Radiat Oncol Biol Phys. 1996;35:731–744.)	1996
Point: Hyperthermia with radiation for chest wall recurrences.	Jones EL, Marks LB, Prosnitz LR.	J Natl Compr Canc Netw 2007; 5(3)339–344 .	2007
DEGRO practical guidelines for radiotherapy of breast cancer VI: therapy of locoregional breast cancer recurrences.	Wolfgang Harms, W Budach , J Dunst , P Feyer , R Fietkau , W Haase , D Krug , M D Piroth , M-L Sautter-Bihl , F Sedlmayer , R Souchon , F Wenz , R Sauer , Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO)	Strahlentherapie und Onkologie volume 192, pages 199–208 (2016)	2016
Reirradiation combined with hyperthermia in breast cancer recurrences: overview of experience in Erasmus MC.	Van Der Zee J, De Bruijne M, Mens JW,, Broekmeyer-Reurink MP, Drizdal T, Linthorst M, Van Rhoon GC.	Int J Hyperthermia. 2010;26(7):638-48.	2010
Chestwall recurrences of breast cancer: results of combined treatment with radiation and hyperthermia.	Gonzalez Gonzalez D, van Dijk JD, Blank LE	Radiother Oncol. 1988;12:95–103.	1988
Quality assurance problems in clinical hyperthermia and their impact on therapeutic outcome: a report by the radiation therapy oncology group.	Perez CA, Gillespie B, Pajak T, Hornback NB, Emami D, Rubin P.	Int J Radiat Oncol Biol Phys. 1989;16:551–558.	1989
Multi-institutional review of repeat irradiation of chest wall and breast for recurrent breast cancer.	Wahl AO, Rademaker A, Kiel KD, Jones EL, Marks LB, Croog V, Mc Cormick BM, Hirsch A, Karkar A, Motwani SB, Tereffe W, Yu TK, Sher D, Silverstein J, Kachnic LA, Kesslering C, Freedman GM,	Int J Radiat Oncol Biol Phys. 2008;70:477–484.	2008
Elective re-irradiation and hyperthermia following resection of persistent locoregional breast cancer: A retrospective study.	Oldenborg S, Van Os RM, Van Rij CM, Crezee J, Van de Kamer JB, Rutgers EJT, Geijsen ED, Zum	Int J Hyperthermia 2010; 26: 136–144	2010

	Vörde sive Vörding PJ, Koning CCE, Van Tienhoven G.		
Breast cancer. Introduction.	Jones EL	Int J Hyperthermia.2010;26(7):611.	2010
Hyperthermia with radiation in the treatment of locally advanced head and neck cancer: A report of randomized trial	Nagraj G Huilgol, Sapna Gupta, CR Sridhar	Journal of Cancer Research and Therapeutics - October-December 2010 - Volume 6 - Issue 4	2010
Report of long-term follow-up in a randomized trial comparing radiation therapy and radiation therapy plus hyperthermia to metastatic lymph nodes in stage IV head and neck patients	R Valdagni 1 , M Amichetti	Int J Radiat Oncol Biol Phys . 1994 Jan 1;28(1):163-9.	1994
SURVIVAL BENEFIT OF HYPERTHERMIA IN A PROSPECTIVE RANDOMIZED TRIAL OF BRACHYTHERAPY BOOST + HYPERTHERMIA FOR GLIOBLASTOMA MULTIFORME	PENNY K. SNEED, M.D.,* PAUL R. STAUFFER, M.S.E.E.,* MICHAEL W. MCDERMOTT, M.D..” et A.	International Journal of Radiation Oncology*Biology*Physics, 15 January 1998, Pages 287-295	1998
Hyperthermia and radiotherapy for inoperable squamous cell carcinoma metastatic to cervical lymph nodes from an unknown primary site	M. Amichetti, M. Romano, L. Cristoforetti, R. Valdagni	Journal of Cancer Research and Therapeutics - October-December 2010 - Volume 6 - Issue 4	2010
Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study	Rolf D Issels, Lars H Lindner, Jaap Verweij, et Al. European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG); European Society for Hyperthermic Oncology (ESHO)	Lancet Oncol . 2010 Jun;11(6):561-70	2010
Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-	Renzo Colombo, Andrea Salonia, Zvi Leib, Michele Pavone-Macaluso, Dov Engelstein	BJU int.2011 Mar;107 (6):912-8	2011

muscle-invasive bladder cancer (NMIBC)			
Role of the Combined Regimen with Local Chemotherapy and Mw-Induced Hyperthermia for Non-Muscle Invasive Bladder Cancer Management. A Systematic Review	Colombo R, Moschini M	Urologia 2013 Jul 10;80 (2):112-9	2013
Chemoradiotherapy combined with intracavitary hyperthermia for anal cancer: feasibility and long-term results from a phase II randomized trial.	Kouloulias V1, Plataniotis G, Kouvaris J, Dardoufas C, Gennatas C, Uzunoglu N, Papavasiliou C, Vlahos L	American Journal of Clinical Oncology, 01 Feb 2005, 28(1):91-99	2005
Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer	Danielle F M De Haas-Kock, Jeroen Buijsen, Madelon Pijls-Johannesma, Ludy Lutgens, Guido Lammering, Ghislaine A P G van Mastrigt, Dirk K M De Ruysscher, Philippe Lambin, Jacoba van der Zee	Cochrane Database Syst Rev . 2009 Jul 8;(3):CD006269.	2009
Reirradiation and hyperthermia in rectal carcinoma	Jorine Juffermans , P. Hanssens, +2 authors J. van der Zee	Cancer 2003 Oct 15; 98 (8):1759-66	2003
Pathological complete response and sphincter-sparing surgery after neoadjuvant radiochemotherapy with regional hyperthermia for locally advanced rectal cancer compared with radiochemotherapy alone	Christopher Schroeder , Cihan Gani, Ulf Lamprecht, Claus Hann von Weyhern, Martin Weinmann, Michael Bamberg, Bernhard Berger	Int J Hyperthermia . 2012;28(8):707-14.	2012
Regional hyperthermia added to intensified preoperative chemo-radiation in locally advanced adenocarcinoma of middle and lower rectum	Sergio Maluta, Mario Romano, Stefano Dall'oglio, Michele Genna, Cristina Oliani, Fabio Pioli, Milena Gabbani, Nadia Marciai & Mario Palazzi	Int. J. Hyperthermia, March 2010; 26(2): 108–117	2010
Conformal radiotherapy plus local hyperthermia in patients affected by locally advanced high risk prostate cancer: preliminary results of a prospective phase II study	S Maluta, S Dall'Oglio, M Romano, N Marciai, F Pioli, M G Giri, P L Benecchi, L Comunale, AB Porcaro	Int J Hyperthermia . 2007 Aug;23(5):451-6	2007

Hyperthermia combined with radiation for the treatment of locally advanced prostate cancer: long-term results from Dana-Farber Cancer Institute study 94-153	Mark D Hurwitz 1 , Jorgen L Hansen, Savina Prokopios-Davos, Judith Manola, Qian Wang, Bruce A Bornstein, Kullervo Hynynen, Irving D Kaplan	Cancer . 2011 Feb 1;117(3):510-6	2011
Salvage prostate HDR brachytherapy combined with interstitial hyperthermia for local recurrence after radiation therapy failure	A.M. Kukiełka, M. Hetna, T. Dąbrowski1,et Al.	Strahlentherapie und Onkologie volume 190, pages 165–170 (2014)	2014
Regional hyperthermia and moderately dose-escalated salvage radiotherapy for recurrent prostate cancer. Protocol of a phase II trial	Arndt-Christian Müller , Daniel Zips , Vanessa Heinrich , Ulf Lamprecht , Otilia Voigt , Susen Burock , Volker Budach , Peter Wust , Pirus Ghadjar	Radiat Oncol . 2015 Jul 8;10:138.	2015
Review of radiotherapy and hyperthermia in primary cervical cancer	Martine Franckena	International Journal of Hyperthermia Volume 28, 2012 - Issue 6	2012
Combined use of hyperthermia and radiation therapy for treating locally advanced cervix carcinoma	Lutgens L, van der Zee J, De Ruysscher DK M, Lambin P, Platt J	Cochrane Library 17 March 2010	2010
Gemcitabine and cisplatin combined with regional hyperthermia as second-line treatment in patients with gemcitabine-refractory advanced pancreatic cancer	Katharina Elisabeth Tschoep-Lechner , Valeria Milani, Frank Berger, Nelli Dieterle, Sultan Abdel-Rahman, Christoph Salat, Rolf-Dieter Issels	Int J Hyperthermia . 2013;29(1):8-16	2013
Phase II trial of combined regional hyperthermia and gemcitabine for locally advanced or metastatic pancreatic cancer	Takeshi Ishikawa , Satoshi Kokura, Naoyuki Sakamoto, et Al.	Int J Hyperthermia . 2012;28(7):597-604	2012
Review: The Role of Hyperthermia in Treating Pancreatic Tumors	Martin Roesch and Boris Mueller-Huebenthal	Indian J Surg Oncol. 2015 Mar; 6(1): 75–81.	2015
Regional hyperthermia combined with chemoradiotherapy in	Sergio Maluta, Moshe Schaffer MD, PhD, Fabio Pioli, Stefano Dall'Oglio, Stefano	Strahlentherapie und Onkologie volume 187, Article number: 619 (2011)	2011

primary or recurrent locally advanced pancreatic cancer	Pasetto, Pamela M. Schaffer, Bernard Weber,e Maria Grazia Giri		

Appraisal of selected articles

Title	Randomized trial of hyperthermia and radiation for superficial tumors.	
Authors	Jones EL, Oleson JR, Prosnitz LR,	
Journal	J Clin Oncol. 2005;23:3079–3085.	
Year	2005	
Type of Evidence	Level I	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1
Summary	Jones and colleagues enrolled 109 patients with superficial tumors (70 patients with breast cancer) in a prospective randomized trial comparing irradiation of chest wall recurrences with irradiation and additional hyperthermia. The complete response rate was 66.1 % in the hyperthermia and 42.3 % in the irradiation-only arm. Previously irradiated patients had the greatest incremental gain in complete response: 23.5 % in the non-hyperthermia versus 68.2 % in the hyperthermia arm. No OS benefit was seen.	

Title	Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials—International Collaborative Hyperthermia Group.	
Authors	Vernon CC, Hand JW, Field SB, et al	
Journal	Int J Radiat Oncol Biol Phys. 1996;35:731–744.)	
Year	1996	
Type of Evidence	Level I	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1
Summary	Data regarding the benefit of hyperthermia are supported by a meta-analysis of five randomized trials including 306 patients with advanced primary or recurrent breast cancer (CR 59% in hyperthermia group vs 41% in the radiotherapy alone).Five randomized trials addressing this question were started between 1988 and 1991. In these trials, patients were eligible if they had advanced	

primary or recurrent breast cancer, and local radiotherapy was indicated in preference to surgery. In addition, heating of the lesions and treatment with a prescribed (re)irradiation schedule had to be feasible and informed consent was obtained. The overall CR rate for RT alone was 41% and for the combined treatment arm was 59%, giving, after stratification by trial, an odds ratio of 2.3. The combined result of the five trials has demonstrated the efficacy of hyperthermia as an adjunct to radiotherapy for treatment of recurrent breast cancer.

Title	Point: Hyperthermia with radiation for chest wall recurrences.	
Authors	Jones EL, Marks LB, Prosnitz LR	
Journal	J Natl Compr Canc Netw 2007; 5(3)339–344 .	
Year	2007	
Type of Evidence	Level I	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

The impact of randomized trials led the National Comprehensive Cancer Network (NCCN) to include hyperthermia in the 2007 Breast Cancer Guidelines for recurrent breast cancer. Between July 1994 and July 2001, 122 patients were enrolled. Most patients(70/108) in this trial experienced chest wall recurrences. Based on test dose criteria, 109 patients were deemed heatable and randomized to treatment with no additional heat (i.e., radiation alone) versus additional hyperthermia with radiation. The hyperthermia dose CEM43°C T 90 was defined prospectively based on prior studies,1 and the hyperthermia arm received 10 minutes or more CEM43°C T 90. This was the first study to use the concepts of prospective dose/prescription to hyperthermia, and stringent quality assurance was used. The complete response rate in the hyperthermia arm was 66% versus 42% in the no hyperthermia arm. The odds ratio for complete response was 2.7 (95% CI, 1.2–5.8; P = .02) favoring the hyperthermia arm. These results are similar to those of the meta-analysis. Previously irradiated patients experienced the greatest incremental gain in complete response: 23.5% in the no hyperthermia arm versus 68.2% in the hyperthermia arm.

Title	DEGRO practical guidelines for radiotherapy of breast cancer VI: therapy of locoregional breast cancer recurrences.	
Authors	Wolfgang Harms , W Budach, J Dunst , P Feyer , R Fietkau , W Haase , D Krug , M D Piroth , M-L Sautter-Bihl , F Sedlmayer , R Souchon , F Wenz , R Sauer	
Journal	Strahlentherapie und Onkologie volume 192, pages 199–208 (2016)	
Year	2016	
Type of Evidence	Level I	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

An increasing number of studies on the combination of hyperthermia and reirradiation of the chest wall have been published. Jones and colleagues enrolled 109 patients with superficial tumors (70 patients with breast cancer) in a

prospective randomized trial comparing irradiation of chest wall recurrences with irradiation and additional hyperthermia. The complete response rate was 66.1 % in the hyperthermia and 42.3 % in the irradiation-only arm. Previously irradiated patients had the greatest incremental gain in complete response: 23.5 % in the non-hyperthermia versus 68.2 % in the hyperthermia arm. No OS benefit was seen. The authors concluded that adjuvant hyperthermia resulted in a significant local control benefit in patients with superficial tumors receiving radiation therapy. These data are supported by a meta-analysis of five randomized trials including 306 patients with advanced primary or recurrent breast cancer . The complete remission rate was significantly improved in patients treated with combined radiation and hyperthermia compared to radiation alone (59 vs. 41 %). OS was not improved. On 2016 hyperthermia was included in the German oncological radiotherapy (DEGRO) guidelines for reirradiation in chest wall recurrence of breast cancer: “In previously irradiated patients with a high risk of a second local recurrence after surgical resection or in patients with unresectable recurrences, reirradiation should be strongly considered. Indication and dose concepts depend on the time interval to first radiotherapy, presence of late radiation effects, and concurrent or sequential systemic treatment. In the absence of severe radiogenic stigmata and an appropriate time interval (> 1 year), reirradiation with doses between 45 and 50 Gy is recommended, but should not exceed cumulative doses of 100–110 Gy3 (2-Gy3 equivalent dose). Particularly in previously irradiated patients, combination with hyperthermia can further improve tumor control”.

Title	Reirradiation combined with hyperthermia in breast cancer recurrences: overview of experience in Erasmus MC
Authors	Van Der Zee J, De Bruijne M, Mens JW,, Broekmeyer-Reurink MP, Drizdal T, Linthorst M, Van Rhoon GC.
Journal	Hyperthermia. 2010;26(7):Int J 638-48
Year	2010
Type of Evidence	Level I

Suitaibility Criteria		
	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

Authors reported a better response (79%) of hyperthermia group vs radiotherapy alone (39%) in breast cancer recurrences. These data allowed hyperthermia to be included in the American, Dutch (Dutch Society for Radiation Oncology), and European (ESO-ESMO 2014) guidelines.Since we use 433 MHz for the application of hyperthermia, the results are rather stable. In 1999 Authors published a CR rate of 74% for the total group of patients treated with eight fractions of 4 Gy and eight hyperthermia treatments, 87% for patients with tumours smaller than 30 mm and 65% for patients with larger tumours. With the same reirradiation schedule combined with four hyperthermia treatments, the overall CR rate is 73%; 82% for small tumours and 65% for larger tumours. The median duration of local tumour control is 32 months. In patients treated for a microscopic tumour residual, the local tumour control rate till death or date of last follow up was 83% for the patients who received eight hyperthermia treatments and 84% for those receiving four hyperthermia treatments.They reported second-degree burns in 19% of the patients and third-degree burns in 7% and subcutaneous burns in 3% after eight 433 MHz treatments. In 71 patients who received four treatments they observed second-degree burns in 31%, third-degree burns in 10% and subcutaneous burns in 7%. These side-effects usually

are grade 2 or less according to the Common Terminology Criteria for Adverse Events version 3.0 scoring system. The hyperthermia-induced burns generally cause no pain because of their occurrence at sites of decreased sensitivity.

Title	Chestwall recurrences of breast cancer: results of combined treatment with radiation and hyperthermia.	
Authors	Gonzalez Gonzalez D, van Dijk JD, Blank LE	
Journal	Radiother Oncol. 1988;12:95–103.	
Year	1988	
Type of Evidence	Level II-2	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P2
	Report/Data Collection	R1

Summary

A study by Gonzalez Gonzalez et al. also proved the efficacy of the combined treatment. 35 patients with chest wall recurrences of breast carcinoma received hyperthermia in addition to radiation therapy, which was administered within 30 min of irradiation. A comparison between 9 cases that received radiotherapy only and 9 cases that received RTHT showed response rates of 33.3% (3/9) and 77.7% (7/9), respectively. Hyperthermia was well tolerated without severe complications.

Title	Quality assurance problems in clinical hyperthermia and their impact on therapeutic outcome: a report by the radiation therapy oncology group.	
Authors	Perez CA, Gillespie B, Pajak T, Hornback NB, Emami D, Rubin P.	
Journal	Int J Radiat Oncol Biol Phys. 1989;16:551–558.	
Year	1989	
Type of Evidence	Level I	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

A correlation between tumor diameter and response rate was ascertained soon after in a randomized trial by the Radiation Therapy Oncology Group (RTOG) for the evaluation of hyperthermia as a treatment for superficial tumors, including breast cancer. The results revealed an improvement in response especially for lesions that were less than 3 cm in diameter and had received more than 2 hyperthermia treatments (42.5 °C). The incidence of maintaining a persistent response over 12 months was greater for patients that received RTHT than for those who received radiotherapy only, indicating that the addition of hyperthermia offers a more durable complete response.

Title	Multi-institutional review of repeat irradiation of chest wall and breast for recurrent breast cancer.	
Authors	Wahl AO, Rademaker A, Kiel KD, Jones EL, Marks LB, Croog V, Mc Cormick BM, Hirsch A, Karkar A, Motwani SB, Tereffe W, Yu TK, Sher D, Silverstein J, Kachnic LA, Kesslering C, Freedman GM, Small W Jr.	
Journal	Int J Radiat Oncol Biol Phys. 2008;70:477–484.	
Year	2008	
Type of Evidence	Level II-2	
Suitability Criteria	Device	D2

Suitability Criteria	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

Between 1993 and 2005, 81 patients underwent repeat RT of the breast or chest wall for locally recurrent breast cancer at eight institutions. The median dose of the first course of RT was 60 Gy and was 48 Gy for the second course. The median total radiation dose was 106 Gy (range, 74.4-137.5 Gy). At the second RT course, 20% received twice-daily RT, 54% were treated with concurrent hyperthermia, and 54% received concurrent chemotherapy. The median follow-up from the second RT course was 12 months (range, 1-144 months). Four patients developed late Grade 3 or 4 toxicity. However, 25 patients had follow-up >20 months, and no late Grade 3 or 4 toxicities were noted. No treatment-related deaths occurred. The development of Grade 3 or 4 late toxicity was not associated with any repeat RT variables. The overall complete response rate was 57%. No repeat RT parameters were associated with an improved complete response rate, although a trend was noted for an improved complete response with the addition of hyperthermia that was close to reaching statistical significance (67% vs. 39%, $p = 0.08$). The 1-year local disease-free survival rate for patients with gross disease was 53% compared with 100% for those without gross disease ($p < 0.0001$).

Title	Elective re-irradiation and hyperthermia following resection of persistent locoregional breast cancer: A retrospective study.
Authors	Oldenborg S, Van Os RM, Van Rij CM, Crezee J, Van de Kamer JB, Rutgers EJT, Geijsen ED, Zum Vörde sive Vörding PJ, Koning CCE, Van Tienhoven G.
Journal	Int J Hyperthermia 2010; 26: 136–144
Year	2010
Type of Evidence	Level II-2

	Device	D2
Suitability Criteria	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

Between 1988 and 2001, 78 patients with high risk recurrent breast cancer underwent elective re-RT and HT. All patients received extensive previous treatments, including surgery and high-dose irradiation (#50Gy). Most had received one or more lines of systemic therapy; 44% had been treated for one previous locoregional recurrences. Re-RT typically consisted of eight fractions of 4Gy, given twice weekly. Hyperthermia was added once a week. After a median follow up of 64.2 months, three-year survival was 66%. Three- and five-year local control rates were 78% and 65%. Acute grade 3 toxicity occurred in 32% of patients. The risk of late grade 3 toxicity was 40% after three years. Time interval to the current recurrence was found to be most predictive for local control in univariate and multivariate analysis. The extensiveness of current surgery was the most relevant treatment related factor associated with toxicity. For patients experiencing local recurrence in a previously radiated area, re-irradiation plus hyperthermia following minimisation of tumour burden leads to a high rate of local control, albeit with significant toxicity. The latter might be reduced by a more fractionated re-RT schedule.

Title	Breast cancer. Introduction.
Authors	Jones EL
Journal	Int J Hyperthermia.2010;26(7):611.
Year	2010

Type of Evidence	Level I	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

Jones EL in the introduction of a special issue " Breast cancer" reported the tremendous progress that has occurred in the role of hyperthermia for the treatment of breast cancer. There are at least 6 major randomised trials demonstrating the efficacy of hyperthermia combined with radiotherapy in recurrent chest wall cancer or in advanced cases of breast cancer. The Vernon trial (English), which brought together 5 trials with more than 300 patients, documented a complete response of 59% in the group of patients treated with hyperthermia, compared to 41% in patients treated with radiotherapy only. More recently, Jacoba van der Zee from the Erasmus University in Rotterdam and Ellen Jones from the Duke University (North Carolina) confirmed these data, reporting a better response with hyperthermia of 79% compared to 39% with radiotherapy alone.These data allowed hyperthermia to be included in the American (NCCN 2007), German (DEGRO), Dutch (Dutch Society for Radiation Oncology), and European (ESO-ESMO 2014) guidelines.

Title	Hyperthermia with radiation in the treatment of locally advanced head and neck cancer: A report of randomized trial
Authors	Nagraj G Huilgol, Sapna Gupta, CR Sridhar
Journal	Journal of Cancer Research and Therapeutics - October-December 2010 - Volume 6 - Issue 4
Year	2010

Type of Evidence	Level I	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

A total of 56 patients were randomized to radiation therapy (RT) alone or RT-hyperthermia (RT-HT) arm. Twenty-six patients were included in RT alone arm and 28 patients in the RT-HT arm. Both groups were evenly matched for age, sex, and stage. Patients in both the arms received radiation to a dose of 66-70 Gy in 6.5-7 weeks. Patients in the study group received weekly HT. HT was started after impedance matching to last for 30 minutes.Complete response was seen in 42.4% of RT alone group compare to 78.6% in the HT group. The difference was statistically significant (< 0.05). Kaplan-Meir analysis of survival also showed a significant improvement in favor of RT-HT. No dose limiting thermal burns and excessive mucosal or thermal toxicity were recorded. Radiofrequency (RF) based heating and radical radiation of head and neck cancers is better than in RT alone group. HT should be considered as a valid option wherever the facility for HT is available. This report should infuse greater confidence in radiation Oncologists to practice HT as an adjuvant treatment modality.

Title	Report of long-term follow-up in a randomized trial comparing radiation therapy and radiation therapy plus hyperthermia to metastatic lymph nodes in stage IV head and neck patients

Authors	R Valdagni 1 , M Amichetti
Journal	Int J Radiat Oncol Biol Phys . 1994 Jan 1;28(1):163-9.

Year	1994	
Type of Evidence	Level I	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

The medical records of 41 patients (44 nodes) with advanced locoregional Stage IV squamous cell cancer of the head and neck and randomized to treatment in the period 1985-1986 with irradiation alone (22/23 evaluable nodes) or combined with external hyperthermia (18/21 evaluable nodes), were re-evaluated. The statistically significant difference observed in "early" response (p = 0.0164) in favor of the combined treatment results in improved 5-year actuarial nodal control (p = 0.015). Clinical improvement noted in tumor control positively affects survival, leading to a statistically significant difference in survival at 5 years (p = 0.02). With respect to side effects, no clearly enhanced acute or late toxicity has been found; as severe late effects, two patients with bone necroses possibly related to the combined treatment have been observed. Thermal analysis failed to show a significant correlation between heating parameters and the end points of the study. This report with 5-year follow-up confirms the efficacy and the absence of severe toxicity of the combination of radical radiation and hyperthermia in the treatment of metastatic lymph nodes in Stage IV squamous cell carcinoma of the head and neck.

Title	SURVIVAL BENEFIT OF HYPERTHERMIA IN A PROSPECTIVE RANDOMIZED TRIAL OF BRACHYTHERAPY BOOST + HYPERTHERMIA FOR GLIOBLASTOMA MULTIFORME
Authors	PENNY K. SNEED, M.D.,* PAUL R. STAUFFER, M.S.E.E.,* MICHAEL W. MCDERMOTT, M.D..” CHRIS J. DIEDERICH, PH.D.,* KATHLEEN R. LAMBORN, PH.D.,’ MICHAEL D. PRADOS, M.D.,” SUSAN CHANG, M.D.,* KEITH A. WEAVER, PH.D .,* LAURA SPRY, B.A.,” MARY K. MALEC. B.S.,-i’ SHARON A. LAMB, R.N.,’ BRIGID Voss, R.N.,’ RICHARD L. DAVIS, M.D.,$ WILLIAM M. WARA, M.D.,* DAVID A. LARSON, M.D., PH.D.,*+ THEODORE L. PHILLIPS, M.D.,* AND PHILIP H. GUTIN, M.D.
Journal	International Journal of Radiation Oncology*Biology*Physics Volume 40, Issue 2, 15 January 1998, Pages 287-295

Year	1998	
Type of Evidence	Level I	
Suitability Criteria	Device	D3
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

Adults with newly-diagnosed, focal, supratentorial glioblastoma I 5 cm in diameter were registered postoperativeiy on a Phase H/III randomized trial and treated with partial brain Fadiotherapy to 59.4 Gy with oral hydroxyurea. Those patients whose tumor was still implantable after tel&eraf.ty were randomized to

brachytherapy boost (60 Gy at 0.40-0.60 Gym) + HT for 30 min immediately before and after brachytherapy. Time to progression (TTP) and survival from date of diagnosis were estimated using the Kaplan-Meier method. Results: From 1990 to 1995,112 eligible patients were entered in the trial. Patient ages ranged from 21-78 years mn, 54 years) and KPS ranged from 70-100 (median, 90). Most commonly due to tumor p on or patient refusal, 33 patients were never randomized. Of the patients, 39 were randomized to brachythefsgy ("no heat") and 40 to brachytherapy + HT ("heat"). By intent to treat, TTP and survival were longer for "heat" than "no heat" (p = 0.04 andp = 0.04). For the 33 "no heat" patients and 35 "heat" patients who underwent brachytherapy boost, TTP and survival were significantly longer for "heat" than "no heat" (p = 0.045 andp = 0.02, respectively; median survival 85 weeks vs. 76 weeks; 2-year survival 31% vs. 15%). A multlvtite analysis for these 68 patients adjusting for age and KPS showed that improved survival was signiiic~y associated with randomization to "heat" (p = 0.008; hazard ratio 0.51). There were no Grade 5 toxicities, 2 Grade 4 toxicities (1 on each arm), and 7 Grade 3 toxicities (1 on "no heat" and 6 on the "heat" arm).

Title	Hyperthermia and radiotherapy for inoperable squamous cell carcinoma metastatic to cervical lymph nodes from an unknown primary site	
Authors	M. Amichetti, M. Romano, L. Cristoforetti, R. Valdagni	
Journal	Int J Hyperthermia 2000; 16(1):85-93	
Year	2000	
Type of Evidence	Level II-2	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

Between 1982 and 1993, radiotherapy and local microwave hyperthermia were used to treat 15 patients with metastatic neck nodes from an unknown primary site. The patients had previously undergone only biopsy or fine needle biopsy, and showed no signs of metastases beyond the clavicle. Radiation to the nodes and the potentially primary sites in the head and neck was delivered by a 6 MV linear accelerator or a Cobalt 60 unit, to a total dose of 57.50-74.40 Gy (median 70 Gy). Hyperthermia was added using a BSD 1000 unit at an operating frequency of 280-300 MHz for 2-7 sessions (mean 3.1; median 2) at a desired minimum temperature of 42.5°C. Two patients also received i.v. cisplatin 20 mg/m2/week as a radiosensitizer. Nine patients achieved a complete, and four a partial response for an overall response rate of 86.5%. Acute and late toxicity was mild: four patients experienced pain during hyperthermia, two moist cutaneous desquamation, and one cutaneous necrosis. The actuarial probability of maintaining local control at 5 years is 64.5% and the actuarial overall survival 29%. Five patients developed distant metastases and died of disease, two experienced nodal recurrence and two died of other unrelated causes.

Title	Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study
Authors	Rolf D Issels, Lars H Lindner, Jaap Verweij, Peter Wust, Peter Reichardt, Baard-Christian Schem, Sultan Abdel-Rahman, Soeren Daugaard, Christoph Salat, Clemens-Martin Wendtner, Zeljko Vujaskovic, Rüdiger Wessalowski, Karl-Walter Jauch, Hans Roland Dürr, Ferdinand Ploner, Andrea Baur-Melnyk, Ulrich Mansmann, Wolfgang Hiddemann, Jean-Yves Blay, Peter

	Hohenberger, European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG); European Society for Hyperthermic Oncology (ESHO)	
Journal	Lancet Oncol . 2010 Jun;11(6):561-70	
Year	2010	
Type of Evidence	Level I	
	Device	D2
Suitability Criteria	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

Patients were recruited to the trial between July 21, 1997, and November 30, 2006, at nine centres in Europe and North America. Patients with localised high-risk STS (> or = 5 cm, Fédération Nationale des Centres de Lutte Contre le Cancer [FNCLCC] grade 2 or 3, deep to the fascia) were randomly assigned to receive either neo-adjuvant chemotherapy consisting of etoposide, ifosfamide, and doxorubicin (EIA) alone, or combined with regional hyperthermia (EIA plus regional hyperthermia) in addition to local therapy. Local progression-free survival (LPFS) was the primary endpoint. Efficacy analyses were done by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT 00003052; 341 patients were enrolled, with 169 randomly assigned to EIA plus regional hyperthermia and 172 to EIA alone. All patients were included in the analysis of the primary endpoint, and 332 patients who received at least one cycle of chemotherapy were included in the safety analysis. After a median follow-up of 34 months (IQR 20-67), 132 patients had local progression (56 EIA plus regional hyperthermia vs 76 EIA). Patients were more likely to experience local progression or death in the EIA-alone group compared with the EIA plus regional hyperthermia group (relative hazard [RH] 0.58, 95% CI 0.41-0.83; p=0.003), with an absolute difference in LPFS at 2 years of 15% (95% CI 6-26; 76% EIA plus regional hyperthermia vs 61% EIA). For disease-free survival the relative hazard was 0.70 (95% CI 0.54-0.92, p=0.011) for EIA plus regional hyperthermia compared with EIA alone. The treatment response rate in the group that received regional hyperthermia was 28.8%, compared with 12.7% in the group who received chemotherapy alone (p=0.002). In a pre-specified per-protocol analysis of patients who completed EIA plus regional hyperthermia induction therapy compared with those who completed EIA alone, overall survival was better in the combined therapy group (HR 0.66, 95% CI 0.45-0.98, p=0.038). Leucopenia (grade 3 or 4) was more frequent in the EIA plus regional hyperthermia group compared with the EIA-alone group (128 of 165 vs 106 of 167, p=0.005). Hyperthermia-related adverse events were pain, bolus pressure, and skin burn, which were mild to moderate in 66 (40.5%), 43 (26.4%), and 29 patients (17.8%), and severe in seven (4.3%), eight (4.9%), and one patient (0.6%), respectively. Two deaths were attributable to treatment in the combined treatment group, and one death was attributable to treatment in the EIA-alone group. 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.

Title

Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC)

Authors	Renzo Colombo, Andrea Salonia, Zvi Leib, Michele Pavone-Macaluso, Dov Engelstein	
Journal	BJU int.2011 Mar;107 (6):912-8	
Year	2011	
Type of Evidence	Level I	
	Device	D3
Suitability Criteria	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

To present long-term efficacy data of intravesical thermochemotherapy vs chemotherapy alone with mitomycin-C (MMC) randomly administered to patients with non-muscle-invasive bladder cancer (NMIBC) as an adjuvant treatment after complete transurethral resection. In all, 83 patients with intermediate-/high-risk NMIBC, following complete transurethral resection, were randomly assigned to receive either intravesical thermochemotherapy by means of Synergo® (Medical Enterprises, Amsterdam, The Netherlands) or intravesical chemotherapy alone, for prophylaxis of tumour recurrence. • Two doses of MMC (20 mg dissolved in 50 mL distilled water administered throughout two consecutive sessions) was used as the chemotherapeutic agent in both arms. • In all, 75 patients completed the original study (35 of 42 in the treatment arm, 40 of 41 in the control arm), whose results at minimum 2-year follow-up have already been published. • Recently, the files of these patients have been updated for long-term outcome definition. Data on general health, follow-up examinations, tumour relapse or progression, and cause of death were collected and analysed. Updated complete data collection was available for 65/75 (87%) of the original patients. • The median follow-up for tumour-free patients was 91 months. The 10-year disease-free survival rate for thermochemotherapy and chemotherapy alone were 53% and 15%, respectively (P <0.001). • An intent-to-treat analysis performed to overcome the potential bias introduced by the asymmetrical discontinuation rate still showed a significant advantage of the active treatment over the control treatment. Bladder preservation rates for thermochemotherapy and chemotherapy alone were 86% and 79%, respectively. This is the first analysis of long-term follow-up of patients treated with intravesical thermochemotherapy. The high rate (53%) of patients who were tumourfree 10 years after treatment completion, as well as the high rate (86%) of bladder preservation, confirms the efficacy of this adjuvant approach for NMIBC at long-term follow-up, even in patients with multiple tumours.

Title	Role of the Combined Regimen with Local Chemotherapy and Mw-Induced Hyperthermia for Non-Muscle Invasive Bladder Cancer Management. A Systematic Review	
Authors	Colombo R, Moschini M.	
Journal	Urologia 2013 Jul 10;80 (2):112-9	
Year	2013	
Type of Evidence	Level I	
	Device	D3
Suitability Criteria	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

The review process followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. An electronic search of the

Medline, Embase, Cochrane Library, CancerLit, and ClinicalTrials.gov databases was undertaken. Relevant conference abstracts and urology journals were also included. The primary end-point was the time to recurrence. Secondary end-points included time to progression, bladder preservation rate, and adverse event (AE) rate.A total of 24 studies met inclusion criteria and underwent data extraction. When feasible, data were combined using random-effects meta-analytic techniques. Recurrence was seen 59% less after CT-MwHT than after MMC alone, however, due to the short follow-up, no definitive conclusions can be drawn about the impact on the time to recurrence and progression. The overall bladder preservation rate after CT-MwHT was 87.6%. This rate appeared higher than after MMC alone, but valid comparison studies could not be drawn due to the absence of randomized trials in neo-adjuvant settings. AEs were higher with CT-MwHT than with MMC alone, but this difference was not statistically significant.
Published data suggest that recurrence rates for chemo-hyperthermia are substantially reduced compared with chemotherapy alone in adjuvant settings. Patients with refractory disease fare worse than those being treated with chemo-hyperthermia for their first tumor. Progression rates to muscle-invasive disease are markedly lower after combination treatment than after chemotherapy alone, with very high rates of bladder preservation. Tolerability is good, with few dropouts in the clinical trials. The results support CT-MwHT in the future as a standard procedure for high-risk recurrent patients, for subjects in whom the treatment with Bacillus Calmette-Guérin is contraindicated, and those unsuitable for radical cystectomy.

Title	Chemoradiotherapy combined with intracavitary hyperthermia for anal cancer: feasibility and long-term results from a phase II randomized trial.
Authors	Kouloulias V1, Plataniotis G, Kouvaris J, Dardoufas C, Gennatas C, Uzunoglu N, Papavasiliou C, Vlahos L
Journal	American Journal of Clinical Oncology, 01 Feb 2005, 28(1):91-99
Year	2005
Type of Evidence	Level I

Suitability Criteria		
	Device	D3
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

The purpose of this study was to investigate in a randomized way the clinical benefit of addition of intracavitary hyperthermia (ICHT) to a conventional chemoradiotherapy schedule in patients with T2-T3N0M0 anal cancer. Patients were randomly assigned to undergo chemotherapy with 5-fluorouracil (5-FU) and mitomycin-C combined with radiotherapy with (arm A: 24 patients) or without ICHT (arm B: 25 patients). A microwave applicator operating at 433 MHz inserted into the anal-rectal cavity was used for ICHT. Patients in both arms received 1000 mg/m2 per day of 5-FU on days 1-4 and days 28-31 plus 15 mg/m mitomycin-C on day 1. Radiotherapy was administered with a dose of 41.4 Gy (1.8 Gy per fraction) plus a booster dose of 14 Gy (2 Gy per fraction).One patient from group A developed severe mucositis, whereas no severe morbidity was noted in the rest of the patients in both groups. The incidence of lower-intestine acute reactions was higher in the ICHT arm. After a 5-year follow up in the hyperthermia arm, 23 of 24 patients (95.8%) preserved their anorectal function and avoided permanent colostomy, whereas in the second arm, 17 of 25 (68.0%)

had sphincter preservation. Local recurrence-free survival time was significantly higher in the ICHT arm (P = 0.0107, log rank test), whereas no significant difference in overall survival was noted. The addition of ICHT to the chemoradiotherapy schedule of anal cancer seems to offer a new effective and safe therapeutic modality. The preservation of anorectal function seems to be the significant clinical benefit of adjuvant ICHT

Title	Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer
Authors	Danielle F M De Haas-Kock 1 , Jeroen Buijsen, Madelon Pijls-Johannesma, Ludy Lutgens, Guido Lammering, Ghislaine A P G van Mastrigt, Dirk K M De Ruysscher, Philippe Lambin, Jacoba van der Zee
Journal	Cochrane Database Syst Rev . 2009 Jul 8;(3):CD006269.
Year	2009
Type of Evidence	Level I

Suitability Criteria		
	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

To quantify the potential beneficial effect of thermo radiation compared to chemo-radiation with respect to pathological complete responses, overall survival and toxicity in rectal cancer therapy. We identified the relevant phase II and III randomised controlled trials in any language trough electronic searches May 2007 of the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 1, 2007), the Cochrane Colorectal Cancer Groups Specialised Register, MEDLINE (from 1966), EMBASE (from 1974), CINAHL (from 1982). Furthermore, various trial databases were searched for the identification of recent completed and ongoing trials (metaRegister of Controlled Trials, Cancer Research UK, Cancer.gov, The Eastern Cooperative Oncology Group Trials Database). All studies identified until May 2007 were considered for inclusion in the present study. Only phase II and III randomised controlled clinical trials were included in the analysis. All identified studies were assessed by two independent reviewers. A weighted estimate of the treatment effect was computed for 2, 3, 4 and 5-year survival, for local tumour recurrence, severe acute and late toxicity and complete tumour response (CR). CR was defined either clinically by disappearance of all pretreatment signs of local tumour or pathologically by microscopically free margins. The risk ratio (RR) and hazard ratio (HR) were used. Analyses were performed with the Reference Manager (RevMan). Six RCTs published between 1990 and 2007 were identified. A total number of 520 patients was treated, 258 in the radiotherapy only arm (RT) and 262 in the radiotherapy-hyperthermia arm (RHT). Four studies (424 patients) reported overall survival (OS) rates. After 2 years, OS was significantly better in the RHT group (HR 2.06; 95% CI 1.33-3.17; p=.001), but this difference disappeared after a longer period (3, 4 and 5 year OS). All but one studies reported CR rates. A significant higher CR rate was observed in the RHT group (RR 2.81; 95% CI 1.22-6.45; p=.01). Only 2 studies reported on acute toxicity. In these 2 studies no significant differences were observed between the RT and the RHT group. Late toxicity data were not reported.

Title	Reirradiation and hyperthermia in rectal carcinoma
Authors	Jorine Juffermans , P. Hanssens, +2 authors J. van der Zee

Journal	Cancer 2003 Oct 15; 98 (8):1759-66	
Year	2003	
Type of Evidence	Level II-2	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

The medical records of 54 patients with unresectable, recurrent colorectal carcinoma that caused pain and who were treated with reirradiation and hyperthermia, were evaluated retrospectively. Previous radiotherapy was given up to a total dose ranging from 25-70 grays (Gy). The median interval between prior radiotherapy and reirradiation was 22 months (range, 4-97 months). The total reirradiation dose varied from 24 Gy to 32 Gy given in fractions of 4 Gy twice weekly. Three or four hyperthermia treatments were given once weekly. Toxicity was registered. The influence of World Health Organization (WHO) performance status, maximum tumor dimension, and time between first radiotherapy and reirradiation on therapeutic outcome was evaluated. The results of this study were compared with published results on patients who received radiotherapy with or without hyperthermia.
Forty-seven patients (87%) completed the planned treatment schedule. The maximum toxicity was Grade 2. All patients were evaluated for palliative effect. The median follow-up was 10 months. A good or complete palliative effect was achieved in 72% of patients for a median duration of 6 months. Patients who had a better WHO performance status, smaller tumors, and a longer interval between first radiotherapy and reirradiation had slightly better outcomes, although none of those parameters reached statistical significance.

Title	Pathological complete response and sphincter-sparing surgery after neoadjuvant radiochemotherapy with regional hyperthermia for locally advanced rectal cancer compared with radiochemotherapy alone	
Authors	Christopher Schroeder 1 , Cihan Gani, Ulf Lamprecht, Claus Hann von Weyhern, Martin Weinmann, Michael Bamberg, Bernhard Berger	
Journal	Int J Hyperthermia . 2012;28(8):707-14.	
Year	2012	
Type of Evidence	Level II-2	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

Between 2007 and 2010, 106 patients with locally advanced cancer of the middle and lower rectum were admitted to neoadjuvant radiochemotherapy either with (n = 61) or without (n = 45) regional hyperthermia. A retrospective comparison was performed between two groups: 45 patients received standard treatment consisting of 5040 cGy in 28 fractions to the pelvis and 5-fluorouracil (RCT group) and 61 patients received the same treatment in combination with regional hyperthermia (HRCT group). Target temperature was 40.5°C for at least 60 min. Total mesorectal excision was performed routinely. pCR was seen in 6.7% of patients in the RCT group and 16.4% in the HRCT group. Patients who received at least four hyperthermia treatments (n = 40) achieved a significantly higher pCR rate (22.5%) than the remaining 66 patients (p = 0.043). Rates of sphincter-

sparing surgery were similar in both groups with 64% in the RCT group and 66% in HRCT. When considering only low-lying tumours located within 8 cm of the anal verge prior to treatment, the rate of sphincter-sparing surgery was 57% in the HRCT group compared with 35% in the RCT group (p = 0.077).The combination of regional hyperthermia and neoadjuvant radiochemotherapy may lead to an increased pCR rate in locally advanced rectal cancer. Patients with low-lying tumours especially may benefit when additional downsizing allows sphincter-preserving surgery.

Title	Regional hyperthermia added to intensified preoperative chemo-radiation in locally advanced adenocarcinoma of middle and lower rectum	
Authors	Sergio Maluta, Mario Romano, Stefano Dall'oglio, Michele Genna, Cristina Oliani, Fabio Pioli, Milena Gabbani, Nadia Marciai & Mario Palazzi	
Journal	Int. J. Hyperthermia, March 2010; 26(2): 108–117	
Year	2010	
Type of Evidence	Level II-2	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

Between June 2000 and April 2006, 76 patients with locally advanced (cT3-4 N0/þ) rectal adenocarcinoma were treated with HT plus CRT. HT was given once a week, to a total of five treatments, 1 to4h after radiotherapy (50Gy with 2-Gy fractions for 5 weeks, plus a 10-Gy boost on the tumour bed, with the same fractionation schedule). Chemotherapy consisted in 5FU 200mg/m2 continuous infusion throughout the 6 weeks of irradiation and OXA 45mg/m2 in a weekly bolus. Surgery followed 4 to 6 weeks after the completion of HT plus CRT. Results: HT plus CRT was generally well tolerated. At pathologic examination, there was a pathologic complete response (pCR) (ypT0 ypN0) in 18 out of 76 patients (23.6%), a partial response (PR) in 34/76 ones (44.7%) and a stable disease (SD) in 20/76 (26.3%) ones; 4/76 patients (5.2%) had a progression disease (PD) (distant metastases) at the time of surgery. Good predictors of a longer disease-free survival (DFS) were in order ypN status (log-rank test: p¼0.0008), ypT status (p¼0.002) and pCR (p¼0.03). Conclusion: Preoperative CRT combined with regional HT yielded acceptable toxicity. The rate of pCR was encouraging, although further studies are needed to prove the long-term efficacy of adding HT to CRT.

Title	Conformal radiotherapy plus local hyperthermia in patients affected by locally advanced high risk prostate cancer: preliminary results of a prospective phase II study	
Authors	S Maluta, S Dall'Oglio, M Romano, N Marciai, F Pioli, M G Giri, P L Benecchi, L Comunale, AB Porcaro	
Journal	Int J Hyperthermia . 2007 Aug;23(5):451-6	
Year	2007	
Type of Evidence	Level II-2	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

Hyperthermia has been used in several trials to treat pelvic cancers without excessive toxicity and with positive results. The aim of this study was to evaluate feasibility and results in terms of biochemical recurrence-free, disease-free survival, overall survival, and treatment toxicity profile of hyperthermia combined with radiotherapy in locally advanced high risk prostate cancer. From November 1998 to December 2004, 144 patients with locally advanced prostate cancer (LAPC) were enrolled in a phase II study. They were treated using conformal radiotherapy (CRT) plus local hyperthermia (LHT) and androgen suppression therapy (AST). Treatment modalities consisted of: 1) CRT with a mean dose of 74 Gy (2 Gy/fraction/5 fractions per week); 2) LHT: one session per week during the first, second, third, and fourth week of the radiotherapy course; 3) AST was administered as neo-adjuvant and adjuvant therapy in more than 60% of patients.The median follow-up time was 51.7 months. Four patients were lost at follow-up. Of 140 evaluated patients, four died because of intercurrent diseases and 12 because of progression of disease. Patients were evaluated in terms of five-year overall survival (87%), and five-year biochemical progression-free survival (49%). No significant side effects, except symptoms related to AST have been reported. No late grade 3 toxicity occurred.In advanced high risk prostatic cancer, hyperthermia is feasible and well tolerated. It may be useful to enhance the radiotherapy efficacy at intermediate dose in order to avoid higher doses of irradiation which increases acute and late sequelae. The advantage of LHT combined with CRT should be confirmed by a randomized phase III trial, comparing irradiation plus AST with or without hyperthermia.

Title	Hyperthermia combined with radiation for the treatment of locally advanced prostate cancer: long-term results from Dana-Farber Cancer Institute study 94-153
Authors	Mark D Hurwitz 1 , Jorgen L Hansen, Savina Prokopios-Davos, Judith Manola, Qian Wang, Bruce A Bornstein, Kullervo Hynynen, Irving D Kaplan
Journal	Cancer 2011 Feb 1;117(3):510-6
Year	2011
Type of Evidence	Level II-3

Suitaibility Criteria		
	Device	D3
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

Patients with clinical T2b-T3bN0M0 disease (according to 1992 American Joint Committee on Cancer [AJCC] criteria) received radiation plus 2 transrectal ultrasound hyperthermia treatments. After the first 4 patients, 6 months of androgen suppression were allowed. The study was designed to assess absolute improvement in the 2-year disease-free survival rate compared with the short-term androgen suppression arm in Radiation Therapy Oncology Group (RTOG) study 92-02. Thirty-seven patients received a total of 72 hyperthermia treatments. The mean cumulative equivalent minutes (CEM) T_{90} 43°C was 8.4 minutes. According to the 1992 AJCC classification, there were 19 patients with T2b tumors, 8 patients with T2c tumors, 5 patients with T3a tumors, and 5 patients with T3b tumors. The median Gleason score was 7 (range, 6-9), and the median prostate-specific antigen (PSA) level was 13.3 ng/mL (range, 2-65 ng/mL). Thirty-three patients received androgen suppression. At a median follow-up of 70 months (range, 18-110 months), the 7-year overall survival rate was 94%, and 61% of patients remained failure free (according to the American

Society for Therapeutic Radiology and Oncology definition for failure free survival). The absolute rate of disease-free survival at 2 years, which was the primary study endpoint, improved significantly (84%) compared with a rate of 64% for similar patients on the 4-month androgen suppression arm of RTOG 92-02. When Phoenix criteria (PSA nadir + 2 ng/mL) were used to define biochemical failure, 89% of patients were failure free at 2 years. Hyperthermia combined with radiation for the treatment of locally advanced prostate cancer appeared to be promising. The current results indicated that further study of hyperthermia for the treatment of prostate cancer with optimal radiation and systemic therapy is warranted.

Title	Salvage prostate HDR brachytherapy combined with interstitial hyperthermia for local recurrence after radiation therapy failure	
Authors	A.M. Kukiełka, M. Hetnał, T. Dąbrowski1, et Al.	
Journal	Strahlentherapie und Onkologie volume 190, pages 165–170 (2014)	
Year	2014	
Type of Evidence	Level II-3	
Suitability Criteria	Device	D3
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

The aim of the present retrospective study is to evaluate toxicity and early clinical outcomes of interstitial hyperthermia (IHT) combined with high-dose rate (HDR) brachytherapy as a salvage treatment in patients with biopsy-confirmed local recurrence of prostate cancer after previous external beam radiotherapy. Between September 2008 and March 2013, 25 patients with local recurrence of previously irradiated prostate cancer were treated. The main eligibility criteria for salvage prostate HDR brachytherapy combined with interstitial hyperthermia were biopsy confirmed local recurrence and absence of nodal and distant metastases. All patients were treated with a dose of 30 Gy in 3 fractions at 21-day intervals. We performed 62 hyperthermia procedures out of 75 planned (83 %). The aim of the hyperthermia treatment was to heat the prostate to 41–43 °C for 60 min. Toxicity for the organs of the genitourinary system and rectum was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE, v. 4.03). Determination of subsequent biochemical failure was based on the Phoenix definition (nadir + 2 ng/ml). The median age was 71 years (range 62–83 years), the median initial PSA level was 16.3 ng/ml (range 6.37–64 ng/ml), and the median salvage PSA level was 2.8 ng/ml (1.044–25.346 ng/ml). The median follow-up was 13 months (range 4–48 months). The combination of HDR brachytherapy and IHT was well tolerated. The most frequent complications were nocturia, weak urine stream, urinary frequency, hematuria, and urgency. Grade 2 rectal hemorrhage was observed in 1 patient. No grade 3 or higher complications were observed. The 2-year Kaplan–Meier estimate of biochemical control after salvage treatment was 74 %. The PSA in 20 patients decreased below the presalvage level, while 11 patients achieved a PSA nadir < 0.5 ng/ml. All patients are still alive. Of the 7 patients who experienced biochemical failure, bone metastases were found in 2 patients. IHT in combination with salvage HDR brachytherapy is a well tolerated and effective treatment.

Title	Regional hyperthermia and moderately dose-escalated salvage radiotherapy for recurrent prostate cancer. Protocol of a phase II trial	
Authors	Arndt-Christian Müller 1 , Daniel Zips 2 , Vanessa Heinrich 3 , Ulf Lamprecht 4 , Otilia Voigt 5 , Susen Burock 6 , Volker Budach 7 , Peter Wust 8 , Pirus Ghadjar	
Journal	Radiat Oncol . 2015 Jul 8;10:138.	
Year	2015	
Type of Evidence	Level II-1	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

The study hypothesis is that radio-thermotherapy is a safe and feasible salvage treatment modality. The primary endpoint is safety measured by frequency of grade 3+ genitourinary (GU) and gastrointestinal (GI) adverse events (AE) according to Common Toxicity Criteria (CTC) version 4. Feasibility is defined by number of hyperthermia treatments (n ≥ 7) and feasibility of radiotherapy according to protocol. Target volume delineation is performed according to the EORTC guidelines. Radiation treatment is administered with single doses of 2 Gy 5×/week to a total dose of 70 Gy. Regional hyperthermia is given 2×/week to a total of 10 treatments. European centres participate in the phase II trial using intensity modulated RT (IMRT) or volumetric modulated arc technique (VMAT). The initiating centres were participants of the SAKK 09/10 study, where the same patient criteria and target volume definition (mandatory successful performed dummy run) were applied insuring a high standardisation of the study procedures. The introduced phase II study implements highly precise image-guided radiotherapy and regional hyperthermia. If the phase II study is found to be safe and feasible, a multicenter phase III study is planned to test whether the addition of regional hyperthermia to dose-intensified sRT improves biochemical control.

Title	Review of radiotherapy and hyperthermia in primary cervical cancer	
Authors	Martine Franckena	
Journal	International Journal of Hyperthermia Volume 28, 2012 - Issue 6	
Year	2012	
Type of Evidence	Level I	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

Six randomised trials have been published comparing radiotherapy to radiotherapy and hyperthermia for primary cervical cancer. The first report appeared in the Indian Medical Gazette in 1987. Datta et al. treated 64 patients with primary cervical cancer FIGO stage IIIb with either radiotherapy alone or combined with hyperthermia. Radiotherapy consisted of 5000–5500 cGy in 25–28 fractions applied over 5–5.5 weeks using a 60Co machine, with a 1000–1500 cGy boost in 5–8 fractions. For hyperthermia treatment delivery, they used a 27-MHz capacitive heating device with external electrodes twice a week after radiotherapy and achieved intravaginal temperatures of 42.5°C for 15 to 20 min per treatment. Response rate, pelvic control and overall survival trended higher

with the addition of hyperthermia to radiotherapy, although the differences did not reach statistical significance. Sharma et al. also used a capacitive heating device, but with an intravaginal electrode. They applied hyperthermia three times a week before radiotherapy and achieved temperatures of 42–43°C at the tumour surface for 30 min. The radiotherapy was delivered using a 60Co machine to apply 45 Gy in 20 fractions over 4 weeks. A boost was delivered using either LDR brachytherapy or 20 Gy in 10 fractions of external beam radiotherapy. Fifty cervical cancer patients were randomised, and in this study pelvic control was improved at 1.5 years follow-up. The first to detect a significant improvement was Chen et al. who randomised 120 patients with cervical cancer FIGO stage IIb and IIIb to receive either radiotherapy alone, radiotherapy combined with chemotherapy, radiotherapy combined with hyperthermia, or radiotherapy combined with both chemotherapy and hyperthermia. As this publication is in Chinese, most of the data is inaccessible, but they found a significant improvement in complete response rate (48% versus 72%) with the addition of hyperthermia . Next, Harima et al. irradiated the whole pelvis to 30.6 Gy in 1.8 Gy fractions and then went on to a total dose of 52.2 Gy after placing a central shield. A boost was delivered to the tumour area using brachytherapy. For hyperthermia, they used an 8 MHz Thermotron capacitive heating device with external electrodes, and randomised 40 patients with cervical cancer FIGO stage IIIb in 2001. They applied three hyperthermia treatments during the period of external beam radiotherapy for 60 min after radiotherapy and achieved intravaginal temperatures of 40.6°C on average. They found a significant improvement in both complete response rate and pelvic control at 3 years follow-up.In 2000 and 2008 reports were published on 114 patients with locally advanced cervical cancer (FIGO IIb–IVa) treated in a multicentre randomised trial, at 3 and 12 years follow-up respectively. Radiotherapy was delivered to a total dose of 46–50.4 Gy in 1.8–2.0 Gy fractions to the tumour area and the pelvic lymph nodes. A brachytherapy boost was applied with either LDR or HDR according to the participating hospital's protocols. For hyperthermia, a radiative system was used once a week for 5 times during the period of external beam radiotherapy. The aim of treatment was to continue for 60 min after the tumour had reached 42°C, to a maximum of 90 min. Power levels were increased to patient tolerance in this trial and an intravaginal temperature of 40.1°C was reached. In these reports, not only response and local control were clearly improved, but also overall survival was significantly better with the addition of hyperthermia. Moreover, this improvement was obtained without adding to long-term toxicity and the results proved to be reproducible in a much larger, unselected group of cervical cancer patients. At 12 years follow-up, an absolute gain in overall survival of 17% was found without increased treatment-related toxicity. In this trial, hyperthermia's cost effectiveness was also determined. Although hyperthermia requires the purchase of a dedicated machine and training of staff members, hyperthermia proved to be very cost effective with the cost per life year gained estimated at €3956. In 2005 the first and only negative report appeared, written by Vasanthan et al. They report on 110 patients staged FIGO IIb to IV treated with a variety of radiation schedules according to the various local treatment protocols using either a 60Co machine or a 6–10 MV linear accelerator. Hyperthermia was applied using an 8 MHz capacitive system with intravaginal electrodes in most patients. They found no difference in local control or survival at 3 years follow-up. However, this study was criticised internationally because of doubts about the adequacy of treatment delivery. Using intravaginal electrodes for heating up the tumour volume, one must keep in mind that very high temperatures can be achieved at the tumour's intravaginal surface, but temperatures may steeply decline at the tumour's periphery. Moreover, we know capacitive heating systems can be used to achieve substantial temperature increases in thin patients, i.e. patients with no more than

2 cm of subcutaneous fat, when the skin is precooled. In this trial, patients with a subcutaneous fat thickness of 3 cm were allowed to participate and precooling of the skin was available in only one of five participating centres. Subcutaneous fat thickness may have been a limiting factor in applying sufficient power in this trial, as in another randomised trial more than twice the power was needed and a beneficial effect was found .Recently, a Cochrane analysis confirmed improved response rates, local control and survival with the addition of hyperthermia to standard radiotherapy, but reservations are made because of the limited number of patients available for analysis, differences in methodology and overrepresentation of patients staged FIGO IIIb. The authors stress that hyperthermia has clear therapeutic benefit in terms of a doubling of the local control rate, improved survival, limited restrictions of its clinical application, and low costs.

Title	Combined use of hyperthermia and radiation therapy for treating locally advanced cervix carcinoma	
Authors	Lutgens L, van der Zee J, De Ruysscher DK M, Lambin P, Platt J	
Journal	Cochrane Library 17 March 2010	
Year	2010	
Type of Evidence	Level II-2	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

We analysed the results of all clinical studies published so far comparing the treatment results of radiotherapy alone with the results of combined radiotherapy and hyperthermia in patients with locally advanced cervix carcinoma. The results do suggest a better outcome for patients treated with the combination of radiotherapy with hyperthermia. Thus following treatment a complete disappearance of the tumour was observed more regularly, regrowth of the tumour at the site of origin during follow up was observed less frequently and more patients were still alive at last follow-up. Treatment related side effects were not increased by the addition of hyperthermia to standard radiotherapy. However, the number of patients included in the clinical studies analysed is limited as the majority of patients had stage IIIB disease. The authors therefore conclude that hyperthermia may provide a clinically relevant improvement in treatment outcome for patients with locally advanced cervix carcinoma, in particular patients with stage IIIB disease. Additional clinical data are needed to warrant its use for all patients with locally advanced cervix carcinoma. The limited number of patients available for analysis, methodological flaws and a significant over-representation of patients with FIGO stage IIIB prohibit drawing definite conclusions regarding the impact of adding hyperthermia to standard radiotherapy. However, available data do suggest that the addition of hyperthermia improves local tumour control and overall survival in patients with locally advanced cervix carcinoma without affecting treatment related grade 3 to 4 acute or late toxicity.

Title Gemcitabine and cisplatin combined with regional hyperthermia as second-line treatment in patients with gemcitabine-refractory advanced pancreatic cancer

Authors	Katharina Elisabeth Tschoep-Lechner 1 , Valeria Milani, Frank Berger, Nelli Dieterle, Sultan Abdel-Rahman, Christoph Salat, Rolf-Dieter Issels	
Journal	Int J Hyperthermia . 2013;29(1):8-16	
Year	2013	
Type of Evidence	Level II-2	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R2

Summary

We retrospectively analysed 23 patients with advanced (n = 2) or metastatic (n = 21) pancreatic cancer with relapse after G mono first-line chemotherapy (n = 23). Patients had received G (day 1, 1000 mg/m(2)) and Cis (day 2 and 4, 25 mg/m(2)) in combination with RHT (day 2 and 4, 1 h) biweekly for 4 months. We analysed feasibility, toxicity, time to second progression (TTP2), overall survival (OS) and clinical response. Between October 1999 and August 2008 23 patients were treated. Haematological toxicity was low with no grade 4 event. Hyperthermia-associated toxicity consisted of discomfort because of bolus pressure (3%), power-related pain (7%) or position-related pain (17%). Median TTP1 was 5.9 months (95% confidence interval (CI): 2.6-9.2), median TTP2 was 4.3 months (95%CI: 1.2-7.4) and OS 12.9 months (95%CI: 9.9-15.9). The disease control rate in 16 patients with available CT scans was 50%.

Title	Phase II trial of combined regional hyperthermia and gemcitabine for locally advanced or metastatic pancreatic cancer	
Authors	Takeshi Ishikawa, Satoshi Kokura, Naoyuki Sakamoto, et Al.	
Journal	Int J Hyperthermia . 2012;28(7):597-604	
Year	2012	
Type of Evidence	Level II-3	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R2

Summary

Eligibility criteria included histologically proven, locally advanced or metastatic pancreatic cancer. Gemcitabine was administered intravenously at a dose of 1000 mg/m(2) on days 1, 8, and 15 every 4 weeks. Regional hyperthermia was performed once weekly, 1 day preceding or following gemcitabine administration. The primary end point was the 1-year survival rate. Secondary objectives were determination of tumour response and safety. We enrolled 18 patients with advanced pancreatic cancer between November 2008 and May 2010. The major grade 3-4 adverse events were neutropenia and anaemia; however, there were no episodes of infection. The objective response rate (ORR) and disease control rate (ORR + stable disease) were 11.1% and 61.1%, respectively. Median overall survival (OS) was 8 months, and the 1-year survival rate was 33.3%. Median OS of patients with locally advanced pancreatic cancer was 17.7 months. Regional hyperthermia combined with gemcitabine is well tolerated and active in patients with locally advanced pancreatic cancer.

Title	Review: The Role of Hyperthermia in Treating Pancreatic Tumors

Authors	Martin Roesch, and Boris Mueller-Huebenthal	
Journal	Indian J Surg Oncol. 2015 Mar; 6(1): 75–81.	
Year	2015	
Type of Evidence	Level II-2	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

This review presents the various methodologies available for hyperthermia, covers the initial clinical data that has been published and gives an outlook to what can be expected in the next 2–3 years to come.
Even though the currently existing data is heterogeneous and in parts methodologically criticizable, still it indicates a clear advantage of adjuvant hyperthermia in prolonging overall survival. Apart from incidences of abdominal pain in the HIPEC method, quality of life is even improved by adding hyperthermia. Expectations are that the ongoing European prospective randomized phase III HEAT trial will yield valuable insight. Though this treatment option is still rather novel and the trials mentioned use different treatment schema, despite all the variations, they all show clear beneficial results indicating the potential that lies in hyperthermia as an additional adjuvant and palliative treatment option.

Title	Regional hyperthermia combined with chemoradiotherapy in primary or recurrent locally advanced pancreatic cancer	
Authors	Sergio Maluta, Moshe Schaffer MD, PhD, Fabio Pioli, Stefano Dall'Oglio, Stefano Pasetto, Pamela M. Schaffer, Bernard Weber,e Maria Grazia Giri	
Journal	Strahlentherapie und Onkologie volume 187, Article number: 619 (2011)	
Year	2011	
Type of Evidence	Level II-2	
Suitability Criteria	Device	D2
	Device Application	A1
	Patient Group	P1
	Report/Data Collection	R1

Summary

Between January 2000 and December 2008, 68 patients affected by primary (56/68) or recurrent (12/68) LAPC were treated either with CRT alone or CRT plus HT. Radiotherapy (RT) consisted of 3D conformal irradiation of tumor and regional lymph nodes (dose ranged from 30 Gy/10 fractions to 66 Gy/33 fractions). Chemotherapy (CT) consisted of gemcitabine (GEM) alone or in association with either oxaliplatin, cisplatin, or 5-FU. HT was delivered twice a week, concomitant with RT. In the current study, 60 of the original 68 patients were included. Median overall survival (OS) was 15 months in the HT group versus 11 months in the control group (log-rank test: $p = 0.025$). HT did not increase CRT toxicity. HT can be added safely to CRT in LAPC, thus, resulting in slightly prolonged survival in certain cases.