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Pharmacoeconomic study of oncothermia (modulated electro-hyperthermia) in the treatment of lung cancer

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Pre-requisites of the study

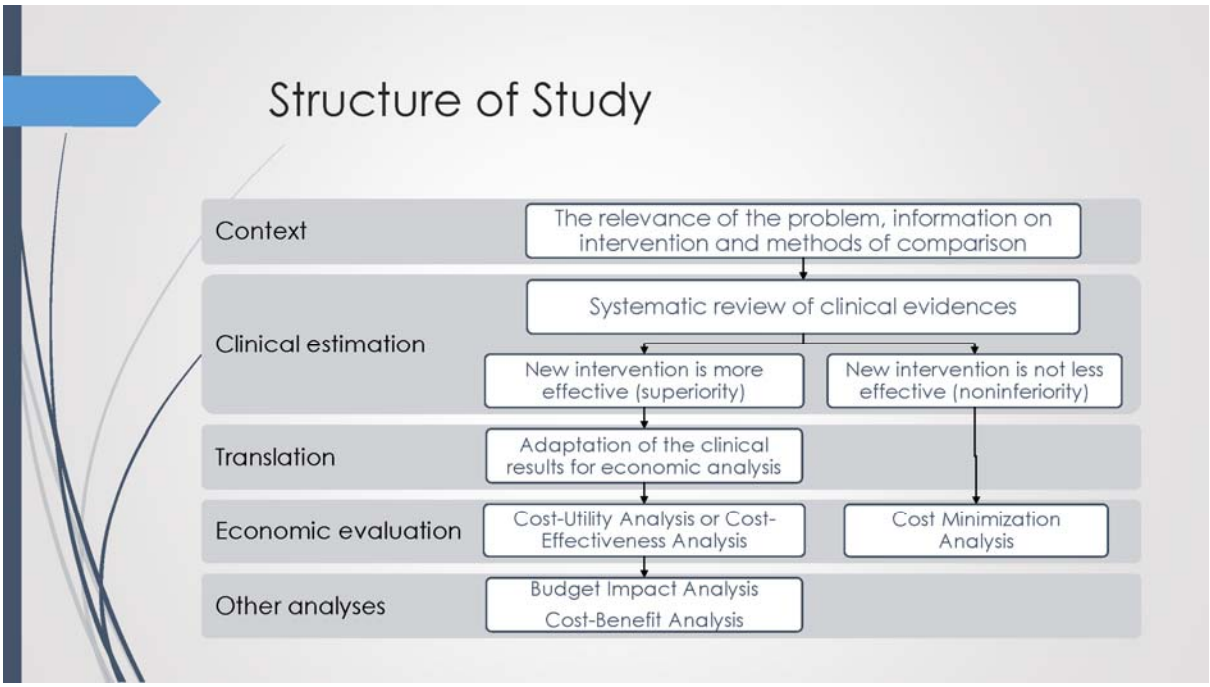
- Lung cancer is a fatal disease with one of the least 5-year survivals among all cancers (14-17% in USA and 12-14% in EU).
- In Russia (2012), share of lung cancer is 18,7% in men and 3,6% in women, and it is the first reason of cancer mortality in Russia (17,3% of all cancer deaths).
- Current treatments show low efficacy and can't change the trend of high mortality.
- Thus, study of possibilities to improve the prognosis in lung cancer is of outstanding significance in oncology.

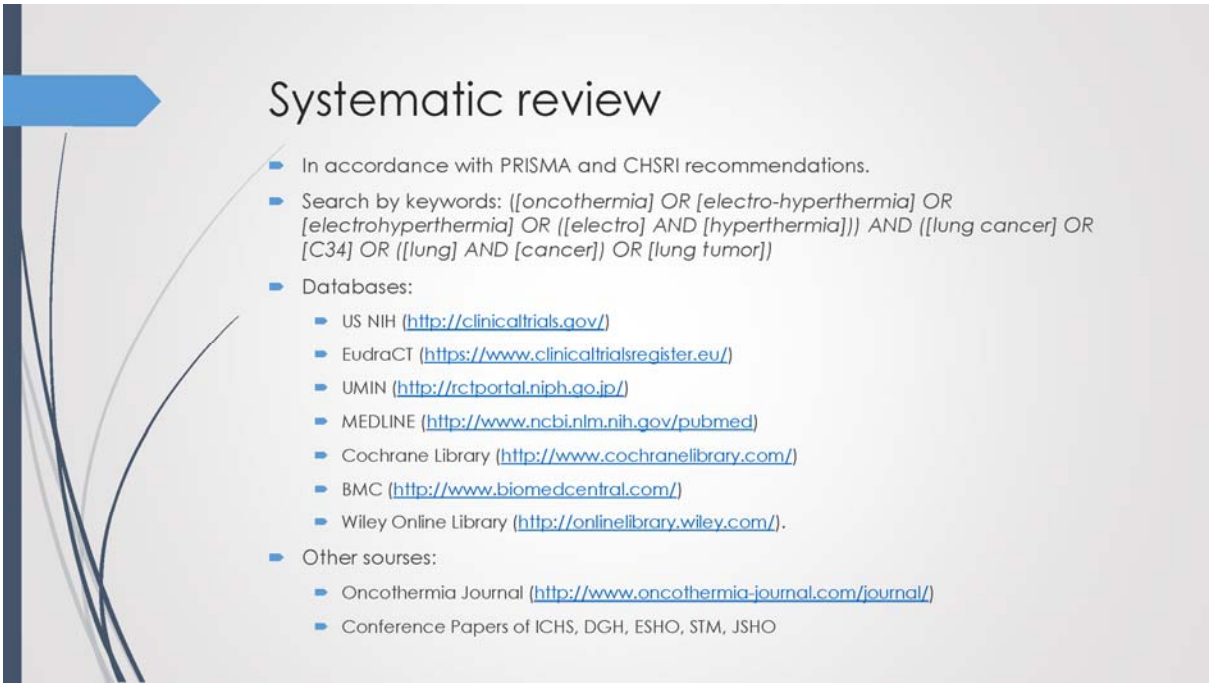
Oncothermia solution

- Oncothermia (local, deep, radiofrequency, modulated electro-hyperthermia) is one of the promising methods of lung cancer treatment.
- This is a new technology based on the local effect of high-frequency electromagnetic field (13.56 MHz), modulated by fractal noise in a range 0-5 kHz, performed by capacitive coupling and functionally asymmetric electrodes.
- The relevance of the present study is determined by the possibility to improve the quality of treatment of lung cancer while reducing health care costs.

Methods

- Retrospective pharmacoeconomical observational study
- Systematic review of oncothermia trials on lung cancer treatment
- Cost-Utility Analysis
- Budget Impact Analysis

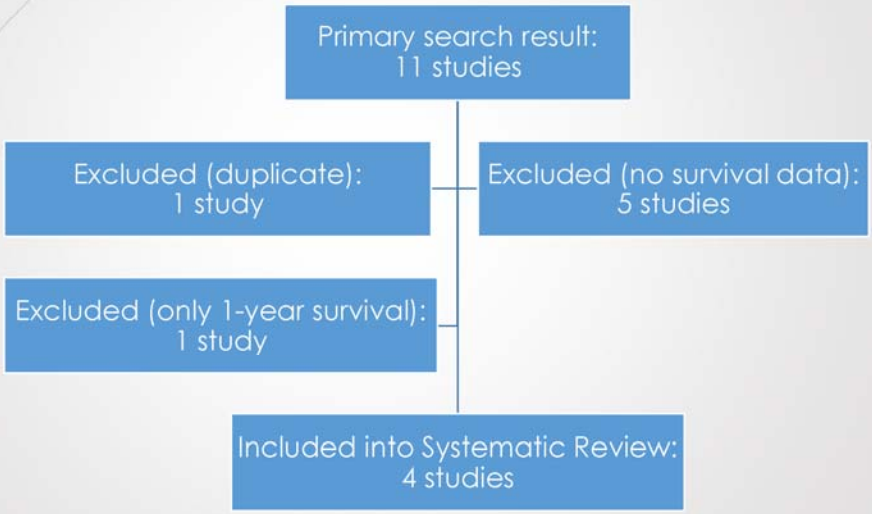

Structure of Study
Context
The relevance of the problem, information on intervention and methods of comparison
Clinical estimation
Systematic review of clinical evidences
New intervention is more effective (superiority)
New intervention is not less effective (noninferiority)
Translation
Adaptation of the clinical results for economic analysis
Economic evaluation
Cost-Utility Analysis or Cost-Effectiveness Analysis
Cost Minimization Analysis
Other analyses
Budget Impact Analysis
Cost-Benefit Analysis


Systematic review
In accordance with PRISMA and CHSRI recommendations.
Search by keywords: ([oncothermia] OR [electro-hyperthermia] OR [electrohyperthermia] OR ([electro] AND [hyperthermia])) AND ([lung cancer] OR [C34] OR ([lung] AND [cancer]) OR [lung tumor])
Databases:
US NIH (http://clinicaltrials.gov/)
EudraCT (https://www.clinicaltrialsregister.eu/)
UMIN (http://rctportal.niph.go.jp/)
MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed)
Cochrane Library (http://www.cochranelibrary.com/)
BMC (http://www.biomedcentral.com/)
Wiley Online Library (http://onlinelibrary.wiley.com/).
Other sourses:
Oncothermia Journal (http://www.oncothermia-journal.com/journal/)
Conference Papers of ICHS, DGH, ESHO, STM, JSHO

Systematic Review: Endpoints

- Primary Endpoints:
  - Overall Survival
- Secondary Endpoint:
  - Health-related Quality of Life (for QALY calculation)

Search Flowchart



Systematic Review: Accepted Studies

Name of Study	Country	Type	NOP	LOE	Publication
Oncothermia with Chemotherapy in the Patients with Small-Cell Lung Cancer	Korea	Prospective, cohort, phase II	31	2b	Lee DY, Haam SJ, Kim TH, Lim JY, Kim EJ, Kim NY. Oncothermia with Chemotherapy in the Patients with Small-Cell Lung Cancer. Conference Papers in Medicine. 2013: Article ID 910363, 7 p. doi:10.1155/2013/910363.
Clinical study for advanced non-small-cell lung cancer treated by oncothermia	Hungary	Retrospective, cohort, phase II	258	2c	Dani A, Varkonyi A, Magyar T, Szasz A. Clinical study for advanced non-small-cell lung cancer treated by oncothermia. Oncothermia J. 2011;3:39-49.
Retrospective matched-group clinical study for advanced NSC lung cancer	Hungary		186	2c	Dani A, Osvath M, Szasz A, Szasz N. Retrospective matched-group clinical study for advanced NSC lung cancer. Hyperthermia symposium Cologne, October 24-25, 2003.
A retrospective assessment of loco-regional hyperthermia and fever-range whole body hyperthermia in an integrative oncology setting	Canada		48	2c	Parmar G. A retrospective assessment of loco-regional hyperthermia and fever-range whole body hyperthermia in an integrative oncology setting. XXXIII Annual Conference of the International Clinical Hyperthermia Society (ICHS). 10-12 Jul 2015, Nidda, Germany.
TOTAL:			458	2a	

CEBM Levels of Evidence (2016)

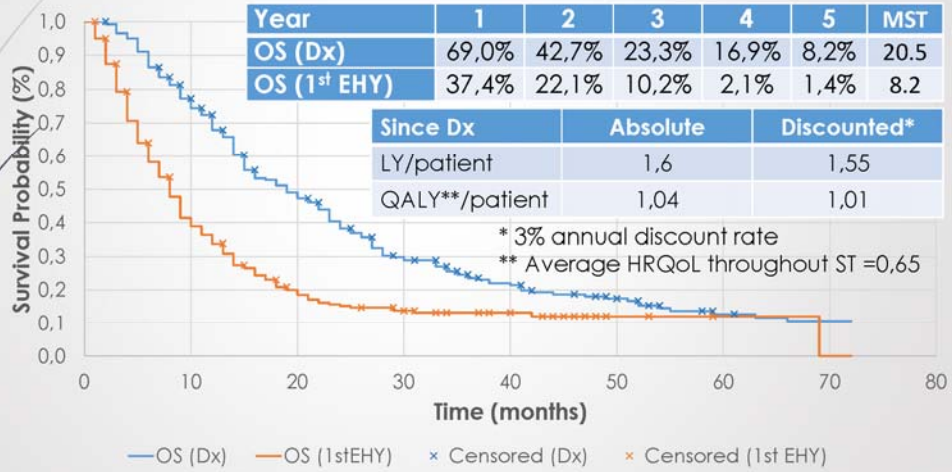
Level	Interventional Studies
1a	Systematic reviews (with homogeneity) of RCTs
1b	Individual RCT (with narrow Confidence Interval)
2a	Systematic reviews (with homogeneity) of Cohort Studies
2b	Individual Cohort Study (including low quality RCT)
2c	"Outcomes" Research
3a	SR (with homogeneity) of Case-Control Studies
3b	Individual Case-Control Study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Analysis of Evidences

Study 1 (Dani et al., 2011): Description

- Retrospective, 2-center, cohort, single arm study
- Non-small cell lung cancer (N=258):
  - Peterfy Hospital (Budapest) (PFY, n=61)
  - HTT-Med Clinic (Budapest) (HTT, n=197)
- Recruitment period: Oct 1997 - Dec 2003
- Average age 57.2±0.65 yrs, median 57 yrs (16-84), normal distribution
- Gender structure: 67.8% males
- Inoperable (St. IIIB-IV): 29% at Dx, 75% at 1st EHY (61% St. IV)
- Oncothermia included in the complex treatment
- Average time to start of oncothermia 11.9±1,07 m, median 6.2 m (0.2-142) or 49.8%±1,8% of OS), median 50.7% (0.68-99)
- Oncothermia applied in the III quartile of survival time

Study 1 (Dani et al., 2011): Survival



Year	1	2	3	4	5	MST
OS (Dx)	69,0%	42,7%	23,3%	16,9%	8,2%	20.5
OS (1st EHY)	37,4%	22,1%	10,2%	2,1%	1,4%	8.2

Since Dx	Absolute	Discounted*
LY/patient	1,6	1,55
QALY**/patient	1,04	1,01

* 3% annual discount rate
** Average HRQoL throughout ST =0,65

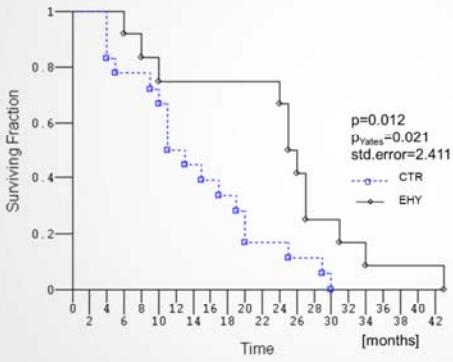
Study 1 (Dani et al., 2011): Quality Control

- Full sample (no exclusions or extractions) – confirmed by check of primary trial documentation
- No inclusion criteria (not limited by Age, Stage of disease or performance status)
- Censoring rate 19% (48/258):
  - Lost during follow-up 11% (28/258)
  - Right-censored (alive to the end of the trial) 8% (20/258)
- Exact death determination by Hungarian Civil Register

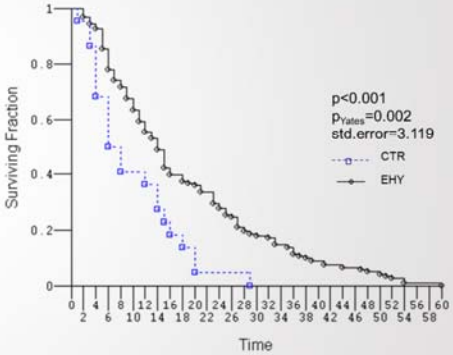
Study 2 (Dani et al., 2003): Description

- Retrospective, monocenter, cohort, double-arm study
- Non-small cell lung cancer (N=186) (Szent Barbala Hispital, Tatabánya):
  - Study arm (SA), standard treatment + oncothermia (n=147)
  - Control arm (CA), standard treatment only (n=39)
- Recruitment period: 1998 - 2001
- Average age: SA=57 yrs, CA=57.3 yrs
- Gender structure: SA=67.8% males, CA=79.2% males
- Metastatic cancer at Dx: SA=59%, CA=45%
- Metastatic cancer at 1st EHY: 88%
- Oncothermia included in the complex treatment

Study 2 (Dani et al., 2003): Survival

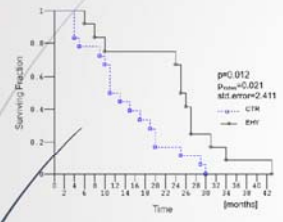


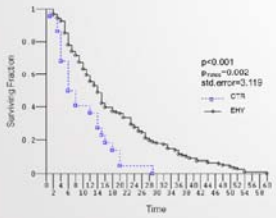
Stage IIIA (n=31/14)



Stage IIIB-IV (n=87/18)

Study 2 (Dani et al., 2003): Survival





Year	1	2	3	4	5	MST
OS (EHY)	58,0%	28,0%	12,0%	5,0%	1,0%	15
OS (Control)	36,0%	4,0%	0,0%	0,0%	0,0%	13.8

Since Dx	Study arm (EHY+)		Control arm (no EHY)	
	Absolute	Disc*	Absolute	Disc*
LY/pat	1,04	1,02	0,4	0,4
QALY**/pat	0,68	0,67	0,26	0,26

* 3% annual discount rate
** Average HRQoL throughout ST: SA=0,65, CA=0.55

Study 3 (Parmar, 2015)

- Retrospective, monocenter, cohort, single arm study
- Integrated Health Clinic (Fort Langley, BC, Canada)
- Non-small cell lung cancer stage IV (N=30)
- Recruitment period: Aug 2010 - Jun 2015
- Stage IV at Dx: 100%
- Oncothermia included in the complex treatment
- Oncothermia applied in the III quartile of survival time

Year	1	2	3	4	5
OS	64,8%	33,5%	33,5%	26,8%	13,4%

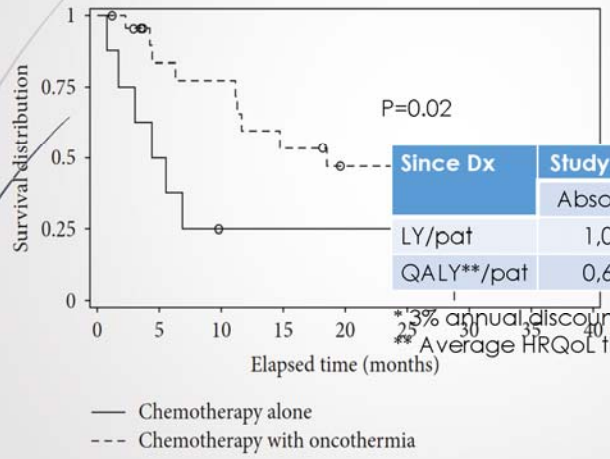
Since Dx	Absolute	Discounted*
LY/patient	1,72	1,65
QALY**/patient	1,12	1,07

* 3% annual discount rate
** Average HRQoL throughout ST =0,65

Study 4 (Lee, 2011): Description

- Prospective, monocenter, cohort, double-arm study
- Gangnam Severance Hospital, Yonsei Unoversity, Korea
- Small cell lung cancer (N=31):
  - Study arm (SA), chemotherapy + oncothermia (n=23)
  - Control arm (CA), chemotherapy only (n=8)
- Recruitment period: ongoing study
- Oncothermia in combination with chemotherapy in 1st-2nd line treatment of SCLC.

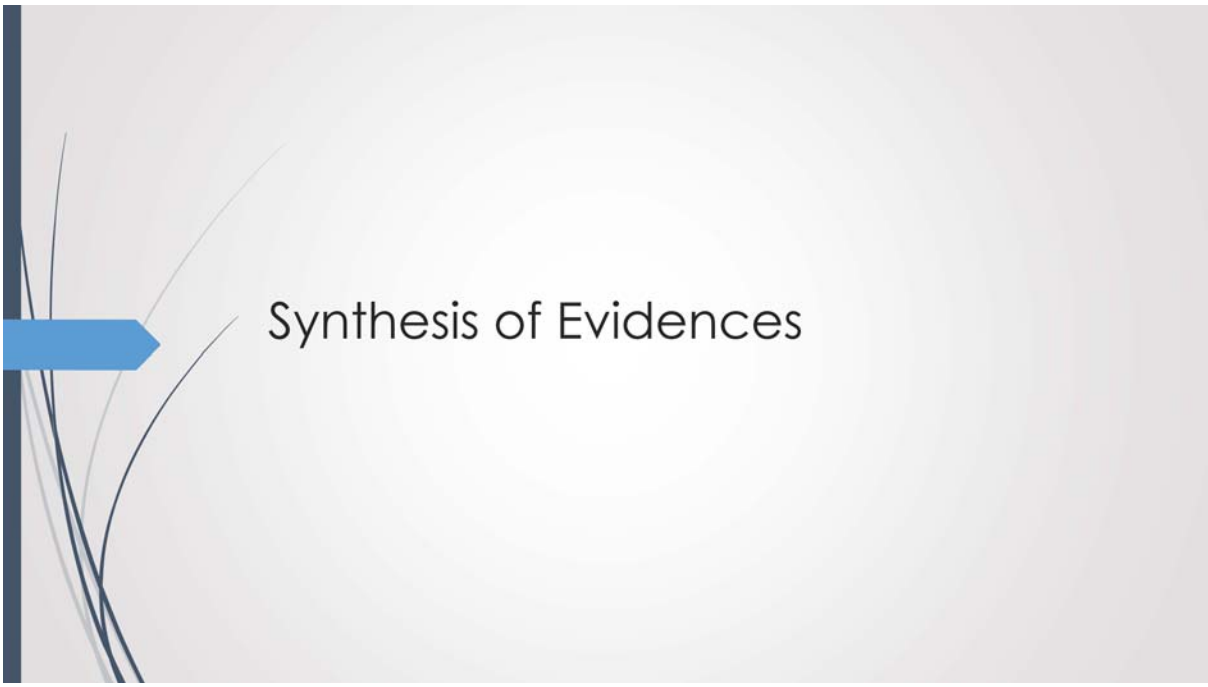
Study 4 (Lee, 2011): Survival

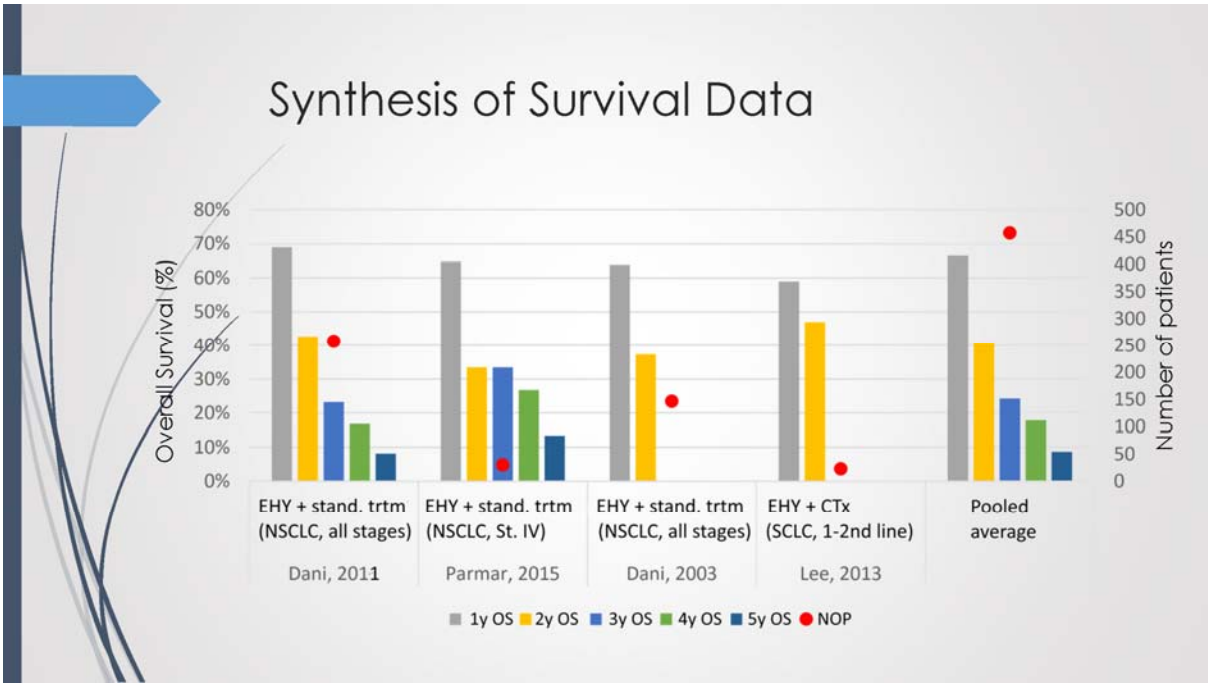


Year	1	2
Study arm	59.0%	47,0%
Control arm	25.0%	25.0%

Since Dx	Study arm (EHY+)		Control arm (no EHY)	
	Absolute	Disc*	Absolute	Disc*
LY/pat	1,06	1,05	0,5	0,49
QALY**/pat	0,69	0,67	0,33	0,3

*3% annual discount rate
** Average HRQoL throughout ST: SA=0,65, CA=0.55

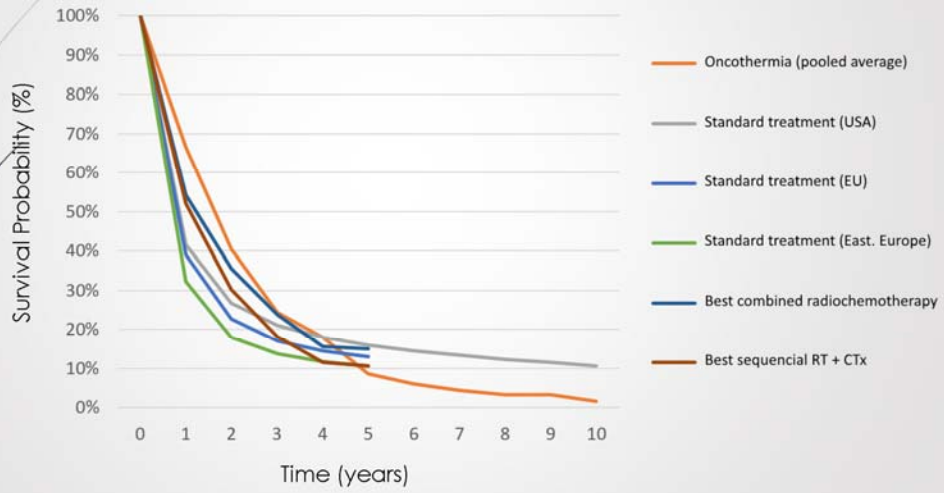

Synthesis of Evidences


Synthesis of Survival Data
Overall Survival (%)
80%
70%
60%
50%
40%
30%
20%
10%
0%
Number of patients
500
450
400
350
300
250
200
150
100
50
0
EHY + stand. trtm (NSCLC, all stages)
EHY + stand. trtm (NSCLC, St. IV)
EHY + stand. trtm (NSCLC, all stages)
EHY + CTx (SCLC, 1-2nd line)
Pooled average
Dani, 2011
Parmar, 2015
Dani, 2003
Lee, 2013
1y OS
2y OS
3y OS
4y OS
5y OS
NOP

Comparison of Overall Survival

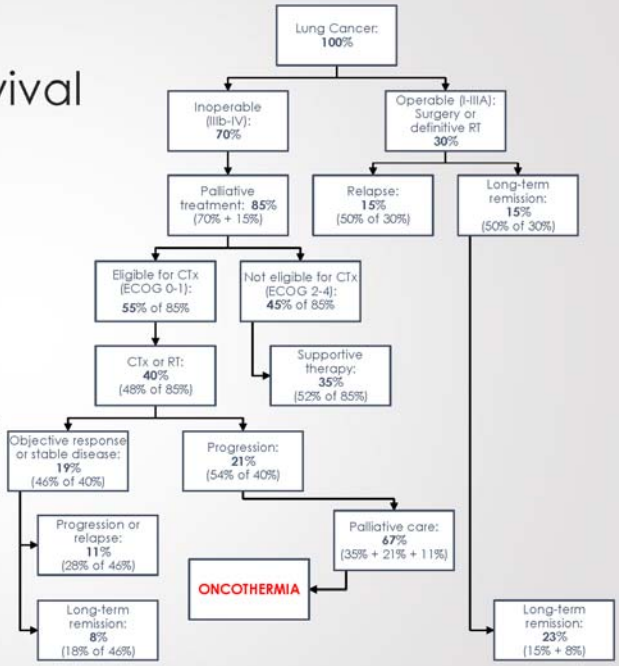
Dataset	1	2	3	4	5
Oncothermia (pooled average)	66,6%	40,6%	24,3%	17,9%	8,7%
Standard treatment USA (SEER)	41,6%	26,8%	21,0%	17,9%	15,9%
Standard treatment EU (Eurocare-5)	39,0%	22,7%	17,1%	14,5%	13,0%
Standard treatment East. Europe (Eurocare-5)	32,4%	18,0%	13,7%	11,7%	10,6%
Best radiochemotherapy	54,2%	35,6%	23,8%	15,6%	15,1%

Comparison of Overall Survival



Why long-term survival drops down?

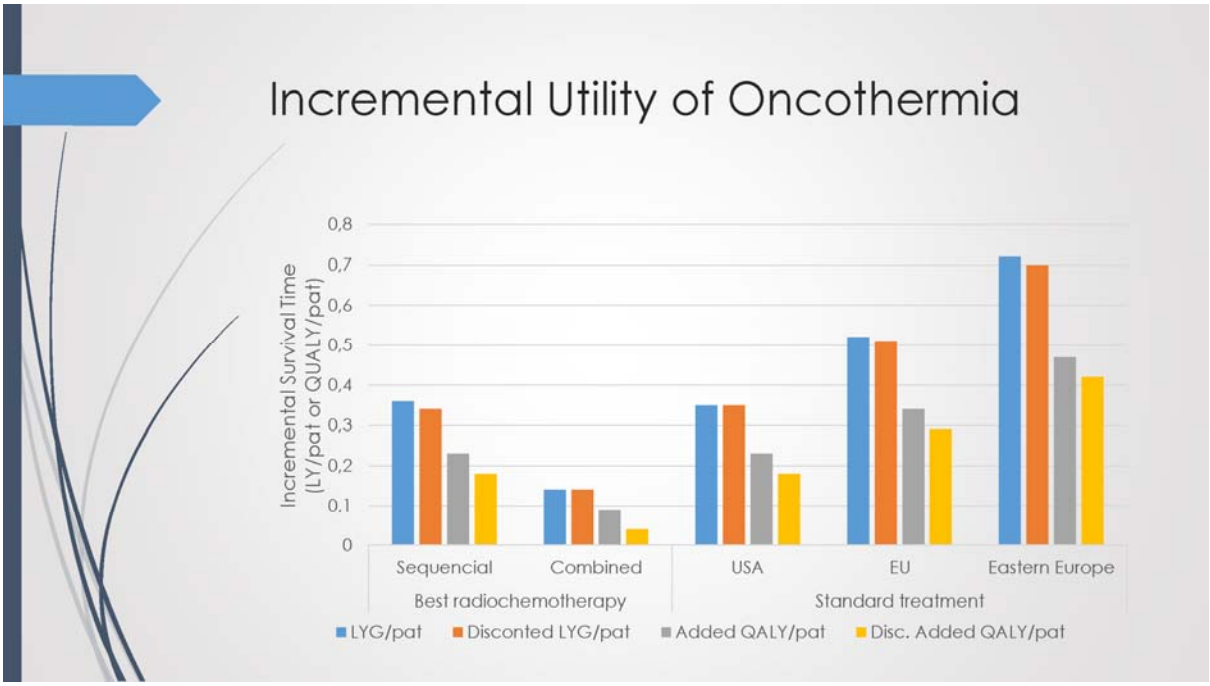
- Currently oncothermia is applied as a 3rd-4th line treatment after fail of the previous treatment, or if other treatment is impossible.
- As such oncothermia sample consists of the patients with poor prognosis:
  - Low performance status (ECOG 2-4) not eligible for CTx and RT;
  - CTX and RT resistant patients;
  - Patients with relapse or progression.
- Oncothermia is used in 3rd quartile of ST, where chances for success significantly lower.
- Effect of basis:
  - Treatment results in USA are 10-20% better than in EU
  - Treatment results in Hungary are 10-20% worse than in EU
  - The main trials were performed in Hungary from 1997 to 2002 (before entrance to EU in 2004), when the treatment quality was even lower.



Incremental Utility of Oncothermia

	Best radiochemotherapy		Standard treatment		
	Sequencial	Combined	USA	EU	Eastern Europe
LYG/pat	0,36	0,14	0,35	0,52	0,72
Disconted LYG/pat	0,34	0,14	0,35	0,51	0,70
Added QALY/pat	0,23	0,09	0,23	0,34	0,47
Disc. Added QALY/pat	0,18	0,04	0,18	0,29	0,42

- Oncothermia provides increment of utility versus all comparators.
- The lesser increment is versus best combined chemoradiotherapy (0,04 QALY/pat)
- The maximal increment is versus Eastern European standard treatment (0,42 QALY/pat)


Incremental Utility of Oncothermia
Incremental Survival Time (LY/pat or QUALY/pat)
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
Sequencial
Combined
USA
EU
Eastern Europe
Best radiochemotherapy
Standard treatment
LYG/pat
Disconted LYG/pat
Added QALY/pat
Disc. Added QALY/pat

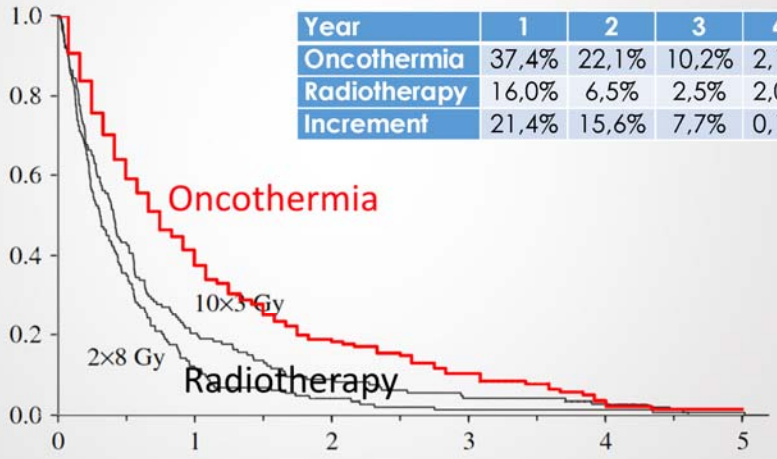

Cost-Utility Analysis
Cost-Utility Analysis of Oncothermia versus Radiotherapy in Treatment of Lung Cancer

Oncothermia vs Radiotherapy: Comparison of cohorts

	Oncothermia	Radiotherapy
Clinical Trial	Dani, 2011	van den Hout, 2006
Country	Hungary	Netherlands
Recruitment	1997-2003	2000-2003
Number of patients	258	297
Average age	**57.4**	69
Males	68%	80%
Stage IV	80%	**47%**
Treatment line	3rd-4th	**1st**
Time to treatment	11.9 months	**1 month**
Pre-treatment	2.69 courses/pat	**0.2 courses/pat**

Oncothermia vs Radiotherapy: Comparison of Survival

Year	1	2	3	4	5
Oncothermia	37,4%	22,1%	10,2%	2,1%	1,4%
Radiotherapy	16,0%	6,5%	2,5%	2,0%	0,0%
Increment	21,4%	15,6%	7,7%	0,1%	1,4%



Oncothermia vs Radiotherapy: Economic Assessment

- Life discounting 3%/year.
- Monetary discounting not used.
- Radiotherapy HRQoL=0.57.
- Though oncothermia always improves life quality versus radiotherapy, the equal HRQoL=0.57 was used for both trials.
- Radiotherapy costs = 3,869 $ /pat.
- Oncothermia costs = 1,727 $/pat:
  - Cost of 1 session EUR 140 (exchange rate 2005 = 1,4 $/EUR).
  - Direct non-medical costs calculated proportionally to radiotherapy costs.

Oncothermia vs Radiotherapy: Cost-Utility Analysis

	QALY/pat	$/pat	CER ($/QALY)
Oncothermia	0.408	1,727	4,230
Radiotherapy	0.151	3,869	25,619
Increment (OT – RT)	0.257	-2,142	-8,328

- **ICER = - 8,328 $/QALY**
- This means that radiotherapy generates $8,238 extra costs per each QALY compared to oncothermia use.

Sensitivity Analysis

- Radiotherapy costs:
  - Average: 8,081 $/pat
  - Median: 8,609 $/pat
  - Minimum: 3,874 $/pat
  - Maximum: 14,491 $/pat
- Oncothermia costs:
  - Minimum: 1,283 $/pat
  - Average: 1,727 $/pat
  - Maximum: 3,095 $/pat (300 EUR/session)
- **ICER = -3,008 — -51,342 $/QALY**
- **Radiotherapy instead of oncothermia generates $3,000 — $50,000 of extra costs per QALY.**

Year	Country	$/pat
2003	Canada	9 060
2005	Netherlands	3 874
1999	Canada	4 086
1999	Canada	5 673
2012	Netherlands	8 291
2012	Netherlands	8 609
2012	Netherlands	9 143
2012	Netherlands	9 503
2012	Netherlands	14 491
	Average	8 081
	Median	8 609
	Minimum	3 874
	Maximum	14 491

Cost-Utility Analysis

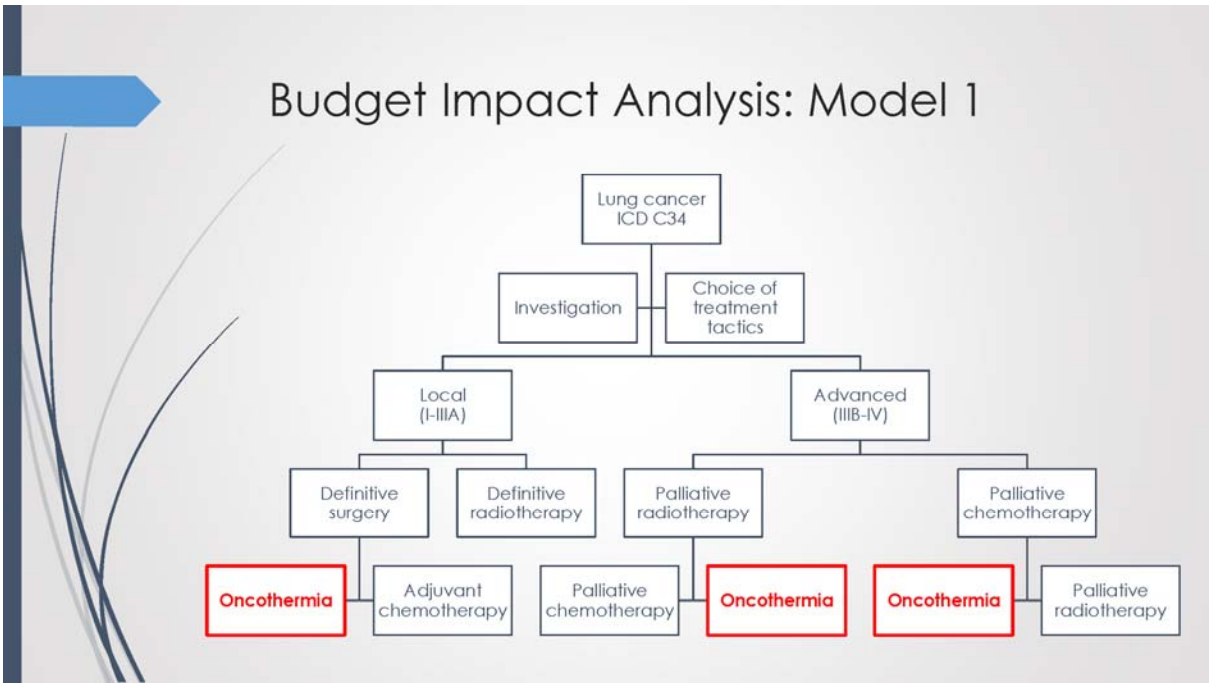
Cost-Utility Analysis of Oncothermia versus Chemotherapy in Treatment of Lung Cancer

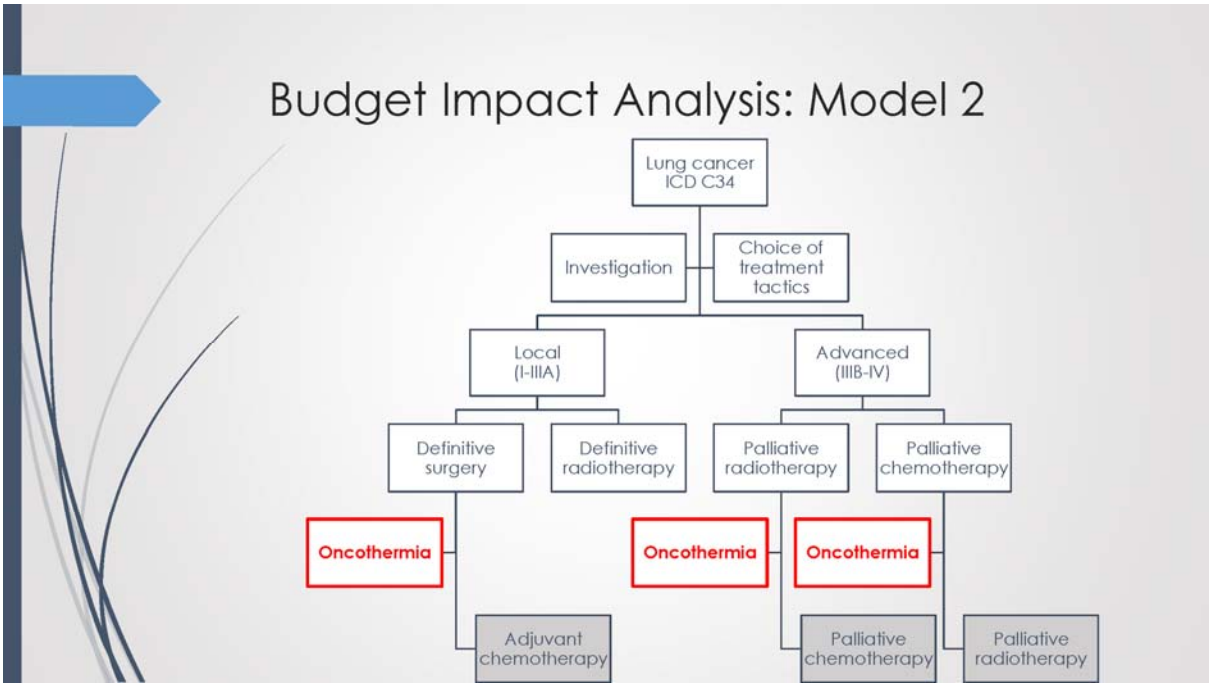
Oncothermia vs Chemotherapy

- Oncothermia of 3rd-4th line versus 1st line Chemotherapy
- Platinum-based Chemotherapy adds 0,49-0,63 LY/pat (average 0,585).
- Chemotherepy costs 5,932-202,176 $/QALY (average 42,841 $/QALY)
- ICER = -10,825 — -250,000 $/QALY
- **Chemotherapy instead of oncothermia generates >$10,000 of extra costs per QALY.**

Chemo	Year	$/unit	Unit	Added units
DOC	2010	48 978	QALY	
DOC	2001	98 493	LY	0,500
DOC	2003	22 181	LY	
DOC	2001	20 654	LY	
DOC (2nd line)	2001	25 442	LY	0,490
DOC средняя		42 412	LY/QALY	
ERL	2014	89 129	QALY	
ERL	2007	202 178	QALY	
ERL	2007	88 030	LY	
ERL	2009	75 710	LY	
ERL	2011	36 838	LY	
ERL average		98 377	LY/QALY	
GEF	2014	56 049	QALY	
GEM	2001	8 251	LY	0,580
GEM	2006	16 603	QALY	
GEM	2002	7 581	PFLY	
GEM+CARB	2014	37 030	QALY	
GEM+CIS	2001	14 559	LY	0,730
GEM+CIS	2014	49 789	QALY	
GEM average		27 123	Разл.	
PAX	2001	43 071	LY	0,540
PAX	2001	67 585	LY	0,540
PAX (135) +CIS	2001	12 379	LY	0,780
PAX (175) +CIS	2001	20 480	LY	0,730
PAX (250) +CIS	2001	17 551	LY	0,830
PAX average		32 213	LY	
PEM	2010	61 470	QALY	
PEM+CIS	2012	56 000	QALY	
PEM average		58 735	QALY	
VIN+CIS	2006	16 603	QALY	
VNB	2001	5 932	LY	0,590
VNB+CIS	2001	7 549	LY	0,700
VNB+CIS	2014	59 797	QALY	
VNB average		24 426	LYS	
CTx average		42 841		0,585
CTx minimum		5 932		0,490
CTx maximum		202 178		**0,626**

Budget Impact Analysis


Budget Impact Analysis: Model 1
Lung cancer ICD C34
Investigation
Choice of treatment tactics
Local (I-IIIA)
Advanced (IIIB-IV)
Definitive surgery
Definitive radiotherapy
Palliative radiotherapy
Palliative chemotherapy
Oncothermia
Adjuvant chemotherapy
Palliative chemotherapy
Oncothermia
Oncothermia
Palliative radiotherapy


Budget Impact Analysis: Model 2
Lung cancer ICD C34
Investigation
Choice of treatment tactics
Local (I-IIIA)
Advanced (IIIB-IV)
Definitive surgery
Definitive radiotherapy
Palliative radiotherapy
Palliative chemotherapy
Oncothermia
Oncothermia
Oncothermia
Adjuvant chemotherapy
Palliative chemotherapy
Palliative radiotherapy

Budget Impact Analysis: Model 2 Pre-requisites

- Utility of conventional chemoradiotherapy cancer treatments averages 0.4 QALY/pat (0.3-0.85 QALY/pat)
- Oncothermia in complex treatment provides the same of higher utility (0.4-1.0 QALY/pat)
- Thus, oncothermia provides enough enhancement of any method from bimodal intervention to substitute the other one.
- Therefore, oncothermia can substitute chemotherapy OR radiotherapy in bimodal intervention.

Budget Impact Analysis: Model 2 Pre-requisites

- Radiotherapy alone is modestly effective in lung cancer treatment but its effect is strongly potentiated by platinum-based chemotherapy.
- At the same time, concurrent chemotherapy increases toxicity of radiotherapy, namely radiation induced lung injury (radiation pneumonitis) and radiation esophagitis.
- With total dose >40 Gy and concurrent chemotherapy, the both radiation-induced lung and esophagus injury are almost inevitable (100%).
- The substitution of chemotherapy by oncothermia can reduce the toxicity and increase survival.

Budget Impact Analysis: Model 2 Pre-requisites

The results of the trial (2012) performed in radiation oncology center of Research Institute named after academician Meshalkin in Novosibirsk (Russia):

- 38 patients with non-small cell lung cancer (all stages) were treated in 2010 by 3D-conformal radiotherapy (total dose 64.25 Gy (equivalent dose 70-76 Gy), single dose 2.75 Gy 5 x week) in combination with oncothermia (10 sessions, 3 x week, 150W x 90 min).
- Beneficial response 95%, including objective response (CR + PR) in 53% and stable disease in 42%; 5% of progression.
- **1-year survival – 97.4%!**

Results

- Oncothermia in the 3rd-4th line complex treatment of lung cancer provided better 1-3 year survival compared to any 1st line conventional treatment except of surgery, including the best chemoradiation treatment.
- Oncothermia provided virtually the same utility as the best concurred chemoradiation treatment (+0,04 QALY/pat) and the better utility than standard treatment in USA and Europe (+0,42 QALY/pat versus Eastern Europe).
- Oncothermia showed the better cost-utility compared to radiation therapy with ICER = -3,000 — -50,000 $/QALY.
- Oncothermia showed the better cost-utility compared to chemotherapy with ICER = -10,000 — -250,000 $/QALY.
- Thus, oncothermia is pharmacoeconomically preferable treatment versus either radiotherapy or chemotherapy in complex treatment of lung cancer.


Thank you for attention