WORKSHOP

La re-irradiazione in ginecologia oncologica

Il contributo delle terapie sistemiche

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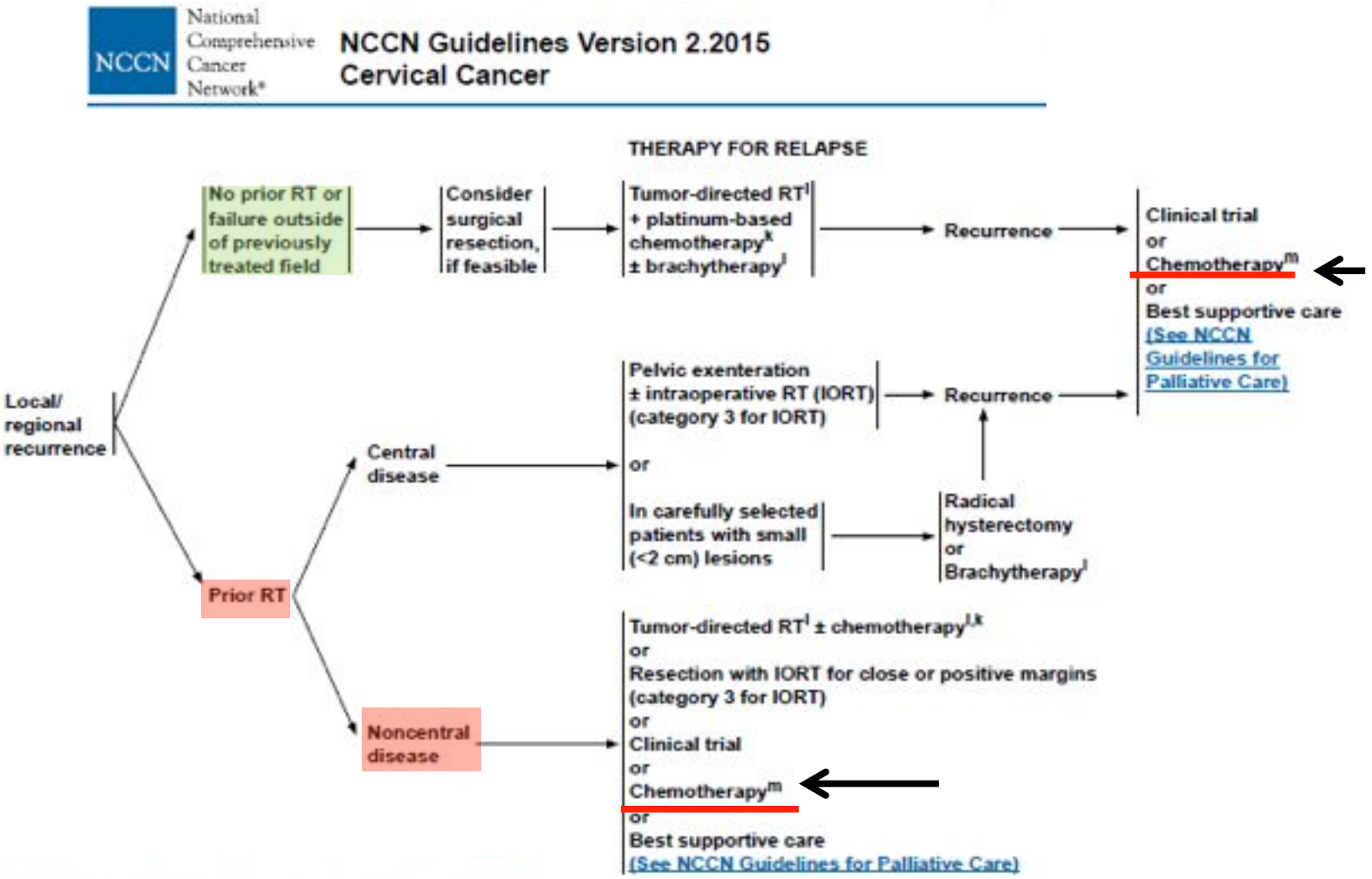
Gemelli ADVANCED RADIATION THERAPY

Chemotherapy which role?

GUIDELINES

Introduction

- **guideline**



http://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf

Introduction

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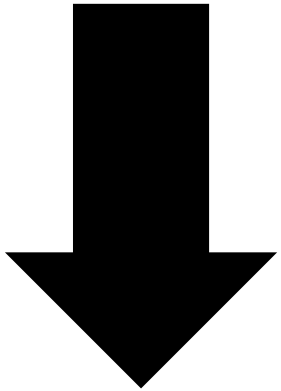
GUIDELINES

Chemotherapy



Palliative Treatment

Chemotherapy which drugs?

Introduction

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phase II trials

- single

GOG trials

phase II: single agent

Table 1. Active single cytotoxic agents for cervical cancer.

Drug	Regimen (mg/m²)	(reference)	Interval (weeks)	Patients (N)	Response rate (%)	Median survival (months)
Cisplatin	50	(Thigpen et al. 1981)	3	34	38	
Carboplatin	340 or 400	(McGuire et al. 1989)	4	175	15	
Oxaliplatin	130	(Fracasso et al. 2003)	3	28	8.3	
Mitomycin-C	20	(Thigpen et al. 1995)	6	56	12	4.9
Ifosfamide	1,200, D1-5	(Sutton et al. 1989)	4	30	11.1	
Paclitaxel	170 or 135	(McGuire et al. 1996)	3	52	17.3	
Paclitaxel	170 or 135	(Curtin et al. 2001)	3	42	31.0	
Docetaxel	100	(Garcia et al. 2007)	3	27	8.7	7.0
Topotecan	1.5, D1-5	(Muderspach et al. 2001)	4	49	18.6	6.4
Topotecan	1.5, D1-5	(Bookman et al. 2000)	3	45	12.5	6.6
Topotecan	3.0, D1, 8 & 15	(Fiorica et al. 2009)	4	27	0	
Irinotecan	125, D1, 8, 15 & 22	(Look et al. 1998)	6	54	13.3	
Gemcitabine	800, D1, 8 & 15	(Schilder et al. 2000)	4	27	8	4.9
Vinorelbine	30, D1 & 8	(Muggia et al. 2004)	3	44	13.7	
Vinorelbine	30, D1 & 8	(Muggia et al. 2005)	3	30	7.1	

D, days.

Seol H-J et al. Tohoku J. Exp. Med. 2014
Leath C.A. et al. Gynecol. Oncol. 2013

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phase II trials

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GOG trials
phase II: doublets

Table 2. Phase II trials of cisplatin-based combination chemotherapy in advanced and recurrent cervical cancer.

Drug & regimen (mg/m^2)	(reference)	Interval (weeks)	Patients (N)	Response rate (%)	Median survival (months)
Cisplatin 50 + 5-FU 1000, D 1-5	(Bononi et al. 1989)	3	55	22	6.4
Cisplatin 50 + Gemcitabine 1250, D 1 & 8	(Burnett et al. 2000)	3	19	41	12 for responders 7 for nonresponders
Cisplatin 30 + Gemcitabine 800, D 1 & 8	(Brewer et al. 2006)	4	32	22	3.5 (PFI)
Cisplatin 50 + Topotecan 0.75, D 1-3	(Fiorica et al. 2002)	3	35	28	10
Cisplatin 75 + Paclitaxel 135	(Rose et al. 1999)	3	47	46	10
Cisplatin 75 + Vinorelbine 30 weekly	(Morris et al. 2004)	4	73	30	5.5 (median response duration)

5-FU, 5-fluorouracil; D, days; PFI, progression-free interval.

Seol H-J et al. Tohoku J. Exp. Med. 2014
Leath C.A. et al. Gynecol. Oncol. 2013

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GOG trials
phase III

Table 3. Phase III trials by the GOG for advanced and recurrent cervical cancer.

Trial (reference)	Drug & regimen	Interval (weeks)	Patients (N)	Response rate (%)	Progression-free interval (months)	Overall survival (months)
GOG 149 (Bloss et al. 2002)	C+IFO vs. C+IFO+B	3	146/141	32/31 (NS)	4.6/5.1 (NS)	8.5/8.4 (NS)
GOG 204 (Monk et al. 2009b)	C+P[a] vs.C+V/C+G/ C+Topo	3	103/108/112/111	29/26/22/23 (NS)	5.8/4.0/4.7/4.6 ($p = -/0.06/0.04/0.19$)	12.9/10.0/10.3/10.3 (NS)
GOG 240 (Tewari et al. 2014)	C+P[b] vs. Topo+P[c]	3	229/223	38/29 (NS)		15/12.5 (NS)

C, cisplatin 50 mg/m²; IFO, ifosfamide 5 g/m²; B, bleomycin 30 units; Topo, topotecan 0.75 mg/m² on days 1-3; V, vinorelbine 30 mg/m² on days 1 and 8; G, gemcitabine 1,000 mg/m² on days 1 and 8; NS, not significant.
[a]paclitaxel 135 mg/m², [b]paclitaxel 135 or 175 mg/m², [c]paclitaxel 175 mg/m².

Doublets:
RR ~ 30%; PFS ~ 5mths; OS < 1 yr

Seol H-J et al. Tohoku J. Exp. Med. 2014
Leath III C.A. et al. Gynecol. Oncol. 2013

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JGOG 0505

CBDCA vs CDDP doublet

	TP	TC
OS (median) HR 0.99 (multiplicity adjusted 90%CI: 0.79-1.25); noninferiority p=0.032	18.3 mo	17.5 mo
PFS (median) HR 1.04 (95%CI: 0.80-1.35)	6.90 mo	6.21 mo
Neutropenia G3-4	85.1%	76.4%
Thrombocytopenia G3-4	3.3%	23.6%
Febrile neutropenia G3-4	16.0%	7.3%
Creatinine G2-4	9.8%	4.1%
Neuropathy (motor) G3-4	0.8%	2.4%
Neuropathy (sensory) G3-4	0%	4.9%
Early treatment discontinuation (toxicity-related)	11.4%	10.0%
NHP (p<0.0001, Wilcoxon rank sum test)	46.4%	61.9%

Doublets:

CBDCA may sobstitute CDDP

Saito J. et al. Jpn.J.Clin.Oncol 2010

Kitagawa R. et al. J.Clin.Oncol. 2012 (abstr)

Gold Standard

CDDP 50 mg/m^2
+
Paclitaxel 75 mg/m^2
every 3 weeks
until PD, CR, tox

Moore D.H. et al. J. Clin. Oncol. 2004
Monk B.J. Et al. J. Clin. Oncol. 2009

New possibilities?

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Gold Standard

new agents

Phase II
new agents

Table 4. Phase II/III trials of targeted agents for advanced and recurrent cervical cancer.

Drug & Regimen	Reference	Interval	Patients (N)	Response rate (%)	Progression-free interval (months)	Median survival (months)
Bevacizumab 15 mg/kg	(Monk et al. 2009a)	3 weeks	46	11	3.4	7.3
Pazopanib 800 mg vs Lapatinib 1,500 mg	(Monk et al. 2010; Monk and Pandite 2011)	Daily/daily	74/78	9/5	4.5/4.3 ($p < 0.013$)	12.4/11.0 ($p = 0.407$)
Sunitinib 50 mg/daily for 4 weeks	(Mackay et al. 2010)	6 weeks	19	0	3.5	
Cetuximab 400 mg/m^2 followed by 250 mg/m^2	(Santin et al. 2011)	Weekly	35	0	2.0	6.7
Cisplatin 30 mg/m^2, D 1 & 8 + Cetuximab 400 mg/m^2 followed by 250 mg/m^2 D 1, 8 & 15	(Farley et al. 2011)	3 weeks	69	12	3.9	8.8
Erlotinib 150 mg	(Schilder et al. 2009)	Daily	28	0	1.9	5.0

D, days.
[a]Cisplatin 50 mg/m^2 + paclitaxel 135-175 mg/m^2 or paclitaxel 175 mg/m^2 + topotecan 0.75 mg/m^2 on days 1-3.

bevacizumab

Seol H-J et al. Tohoku J. Exp. Med. 2014
Leath C.A. et al. Gynecol. Oncol. 2013

GOG-240
phase III beva

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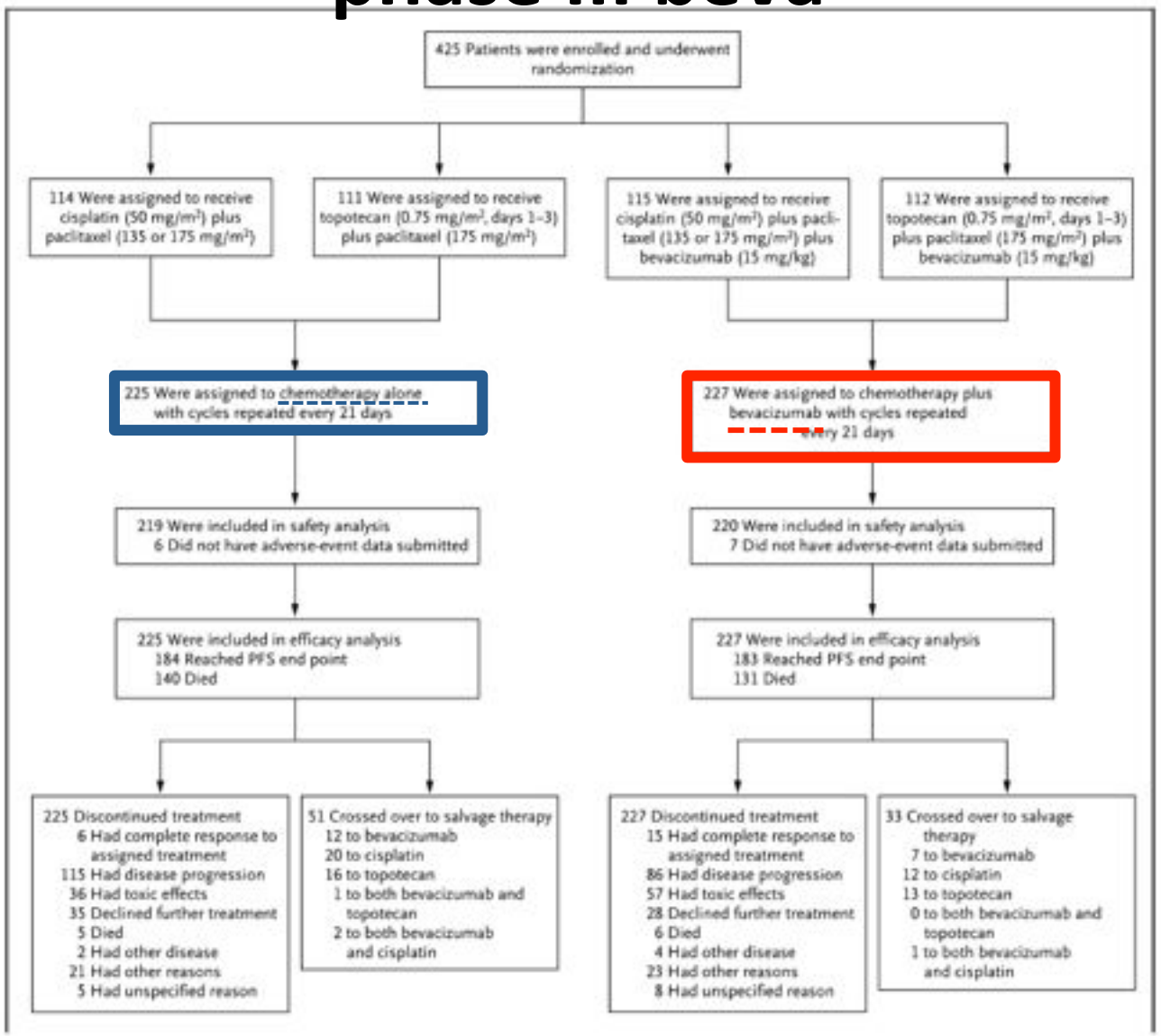
- **CDDP-based**
- **CBDCA**

Gold Standard

new agents

- **beva**



Tewary K.S. et al. N.Engl.J.Med 2014

GOG-240
phase III beva

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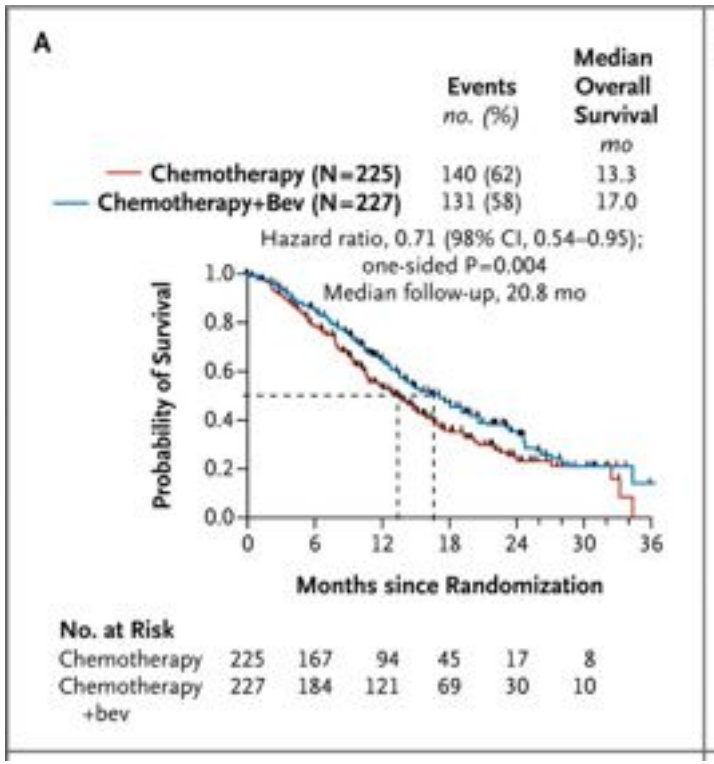
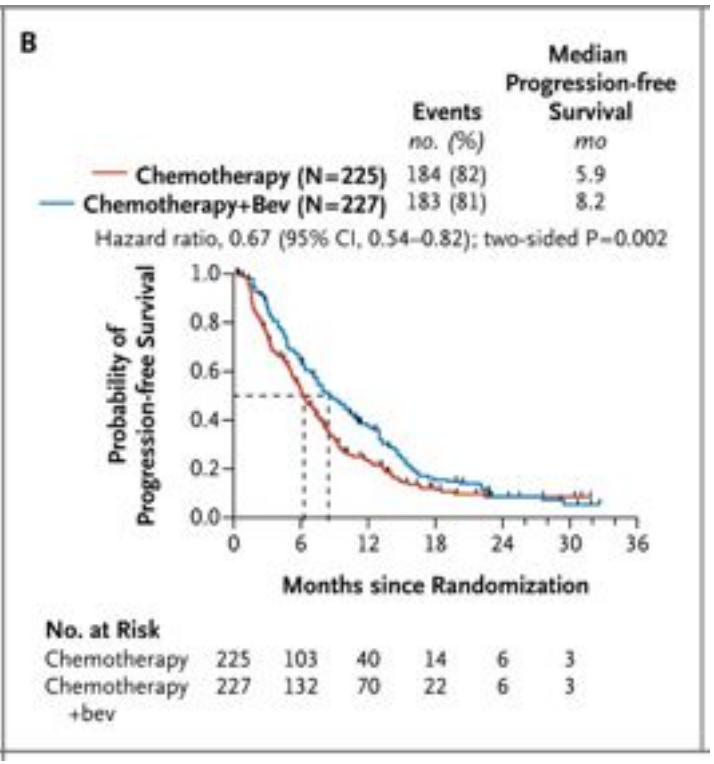
	chemo	chemo+beva	p
Response rate	36%	48%	0.08

OS



PFS



Tewary K.S. et al. N.Engl.J.Med 2014

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GOG-240

phase III beva

Toxicity

Event	Chemotherapy Alone (N = 219)	Chemotherapy plus Bevacizumab (N = 220)	Odds Ratio (95% CI)	P Value
no. of patients (%)				
Gastrointestinal events, excluding fistulas (grade ≥2)	96 (44)	114 (52)	1.38 (0.93–2.04)	0.10
Fistula (grade ≥3)				
Gastrointestinal	0	7 (3)	NA (1.90–∞)	0.02
Genitourinary	1 (<1)	6 (3)	6.11 (0.73–282.00)	0.12
Total[f]	1 (<1)	13 (6)	13.69 (2.01–584.00)	0.002
Hypertension (grade ≥2)[g]	4 (2)	54 (25)	17.50 (6.23–67.50)	<0.001
Proteinuria (grade ≥3)	0	4 (2)	NA (0.90–∞)	0.12
Pain (grade ≥2)	62 (28)	71 (32)	1.21 (0.79–1.85)	0.41
Neutropenia (grade ≥4)	57 (26)	78 (35)	1.56 (1.02–2.40)	0.04
Febrile neutropenia (grade ≥3)	12 (5)	12 (5)	1.00 (0.40–2.48)	1.00
Thromboembolism (grade ≥3)	3 (1)	18 (8)	6.42 (1.83–34.4)	0.001
CNS bleeding (grade ≥3)	0	0	NA	
Gastrointestinal bleeding (grade ≥3)[f]	1 (<1)	4 (2)	4.04 (0.39–200.00)	0.37
Genitourinary bleeding (grade ≥3)[f]	1 (<1)	6 (3)	6.11 (0.73–282.00)	0.12

Tewary K.S. et al. N.Engl.J.Med 2014

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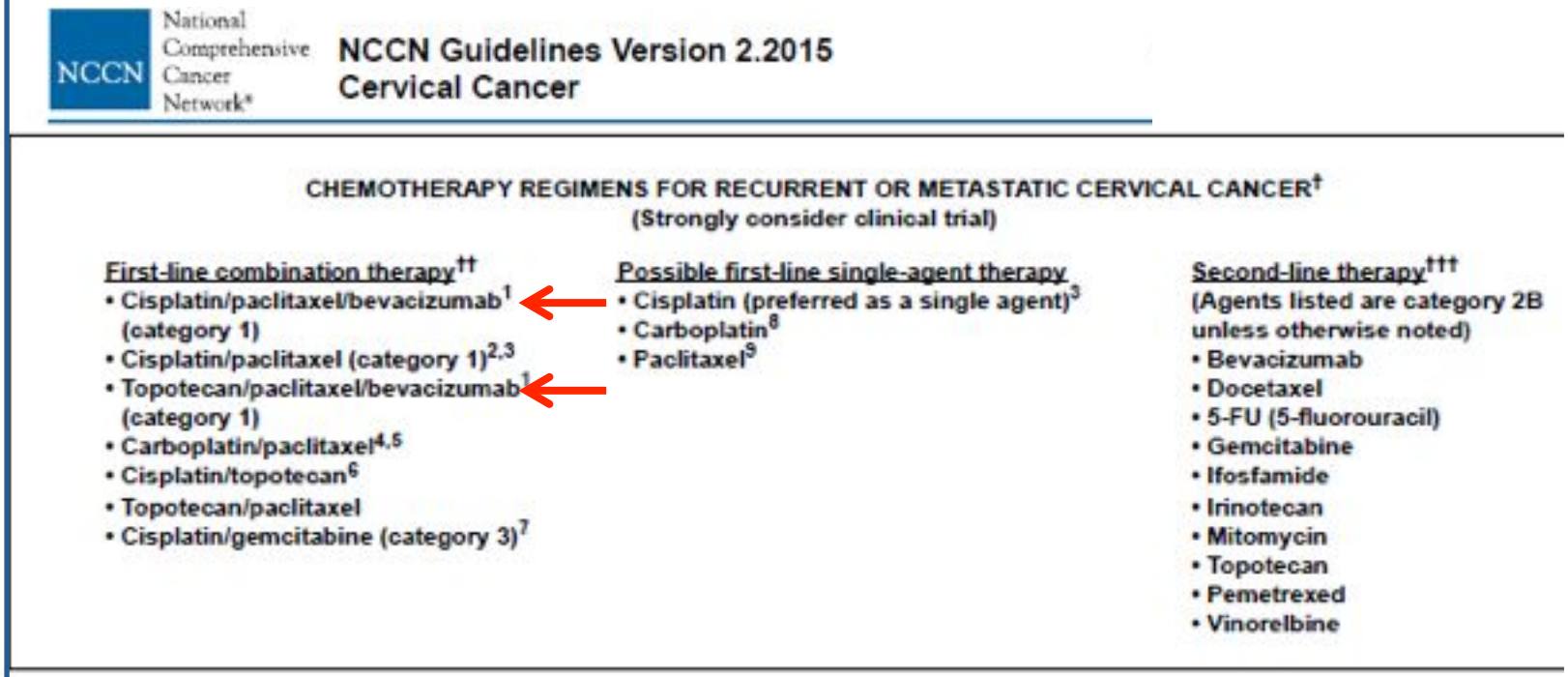

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Cervical Cancer

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC CERVICAL CANCER†
(Strongly consider clinical trial)

First-line combination therapy††
- Cisplatin/paclitaxel/bevacizumab[1] (category 1)
- Cisplatin/paclitaxel (category 1)[2,3]
- Topotecan/paclitaxel/bevacizumab[1] (category 1)
- Carboplatin/paclitaxel[4,5]
- Cisplatin/topotecan[6]
- Topotecan/paclitaxel
- Cisplatin/gemcitabine (category 3)[7]

Possible first-line single-agent therapy
- Cisplatin (preferred as a single agent)[3]
- Carboplatin[8]
- Paclitaxel[9]

Second-line therapy†††
(Agents listed are category 2B unless otherwise noted)
- Bevacizumab
- Docetaxel
- 5-FU (5-fluorouracil)
- Gemcitabine
- Ifosfamide
- Irinotecan
- Mitomycin
- Topotecan
- Pemetrexed
- Vinorelbine

http://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf

Chemo to any patient?

Prognostic factors

Chemo (428 pts GOG 110-169-179 e GOG 149)

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- chemo

	No. patients	Response (%)	P value
Age group (years)			0.175
≤50	240	29.2	
>50	169	35.5	
Race			0.029
White	258	36.7	
Black	107	21.5	
Other	44	34.1	
Performance status			0.023
0	126	41.3	
1	110	27.3	
2	173	27.8	
Stage			0.848
IVB/persistent	65	30.8	
Recurrent	344	32.0	
Histology			0.054
Squamous	391	32.7	
Other	18	11.1	
Tumor grade			0.944
1	16	31.3	
2	231	32.5	
3	162	30.9	
Site of disease			0.021
Pelvic	183	28.4	
Distant	173	38.7	
Combined	53	20.8	
Prior radiosensitizer			0.008
Yes	141	23.4	
No	268	36.2	
1st Recurrence within 1 year since diagnosis			0.007
Yes	191	25.1	
No	218	37.6	
Chemotherapy within 4 weeks since 1st recurrence			0.689
Yes	208	32.7	
No	201	30.9	
Total	409	31.8	

RACE
Later stage presentation
Undertreatment
Nutritional status
Smoking behaviour

SITE of recurrence

Prior RT-CT
Bone Marrow function
Drug distribution
Renal dysfunction
More resistant

Moore DH et al. Gynecol. Oncol. 2010

Prognostic factors
chemo

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Risk Factors
1. **RACE: black**
2. **PS: 1-2**
3. **SITE: pelvic**
4. **Time Rec: < 1yr**
5. **Prior RT-CT**

Low risk: 0-1 risk factors

Mid-risk: 2-3 risk factors

High-risk: 4-5 risk factors

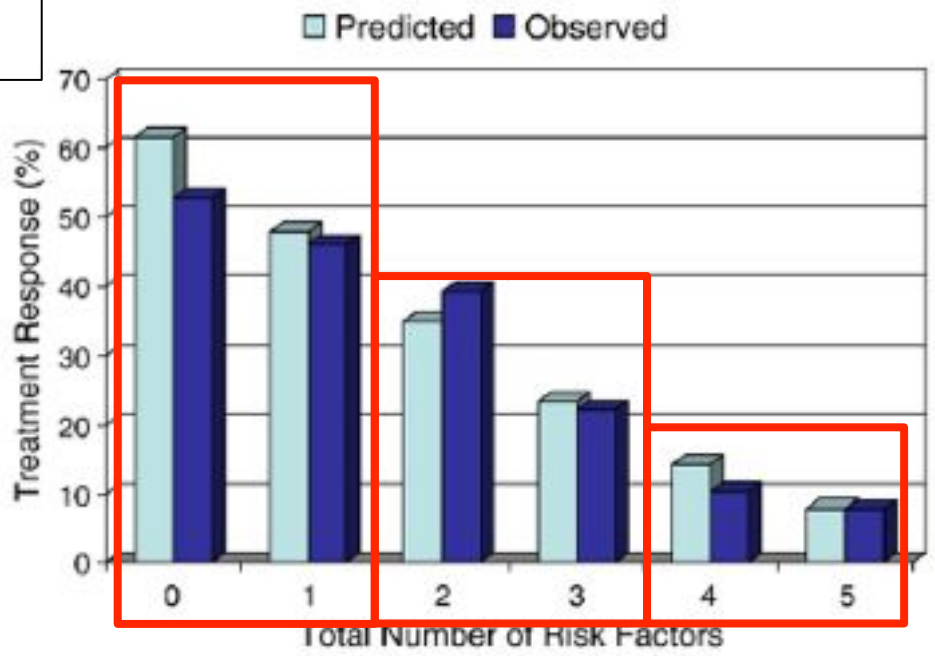

Fig. 1. Predicted and observed response rate by number of risk factors.

Moore DH et al. Gynecol. Oncol. 2010

Prognostic factors
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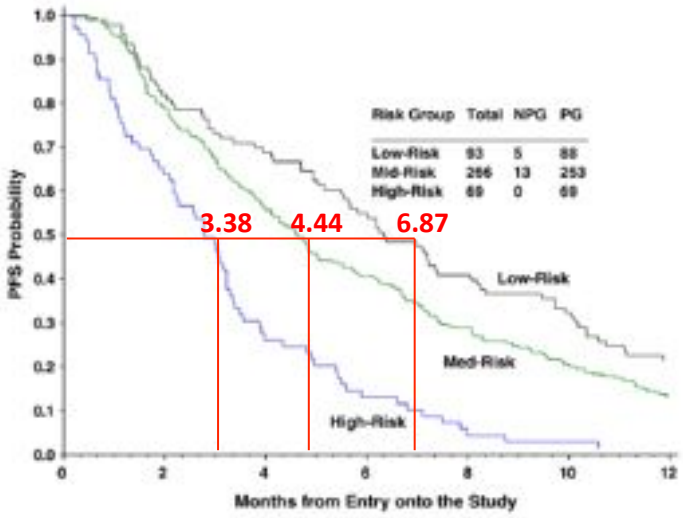
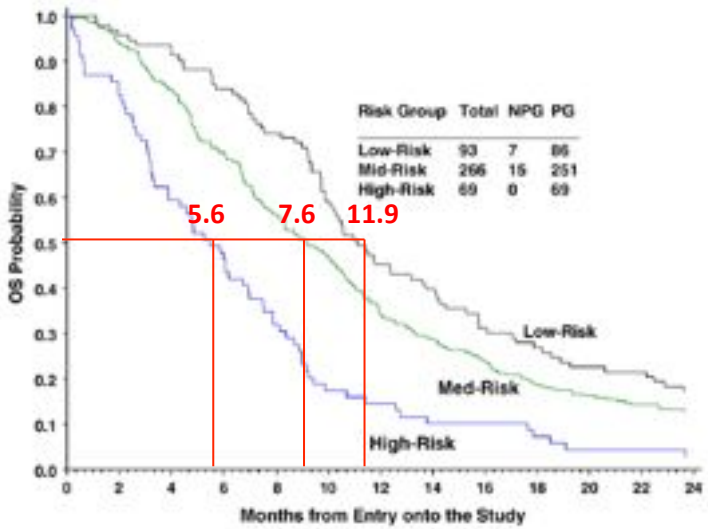


High-risk: 4-5 risk factors

16% of the entire population with

RR 13%, median **OS 5.6 months**



Moore DH et al. Gynecol. Oncol. 2010

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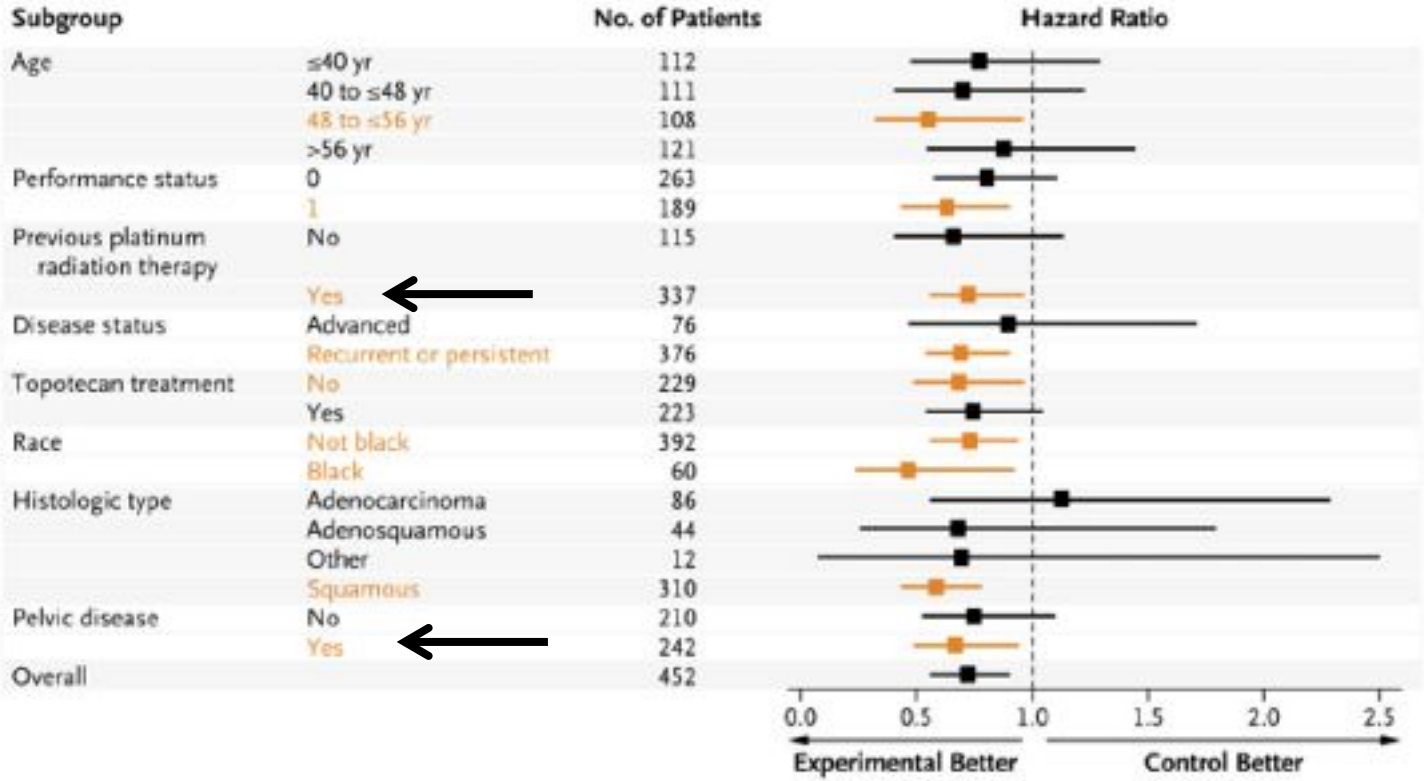

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Chemo at any cost?

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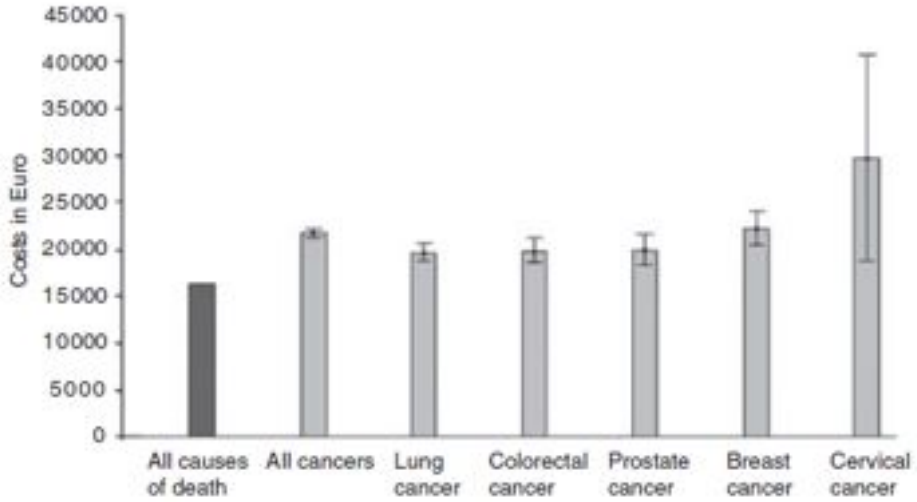
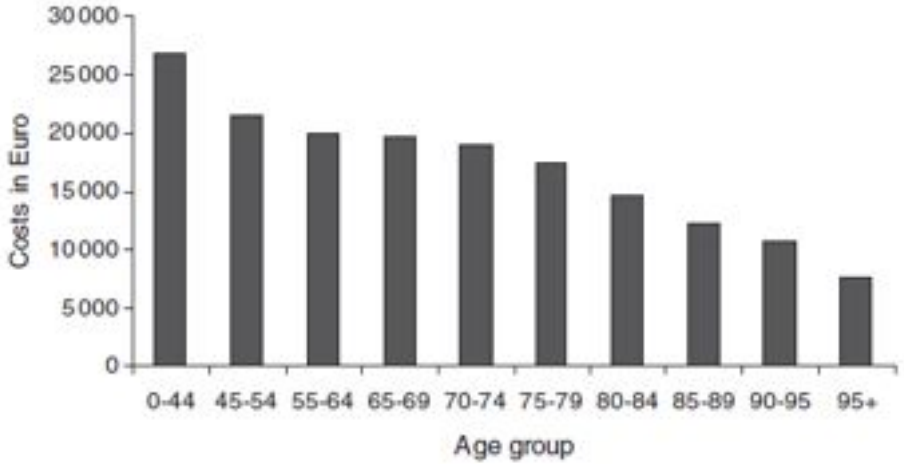
cost-analysis

Cost-analysis:

last year of life





de Kok I.M. et al. Br. J. Cancer 2009

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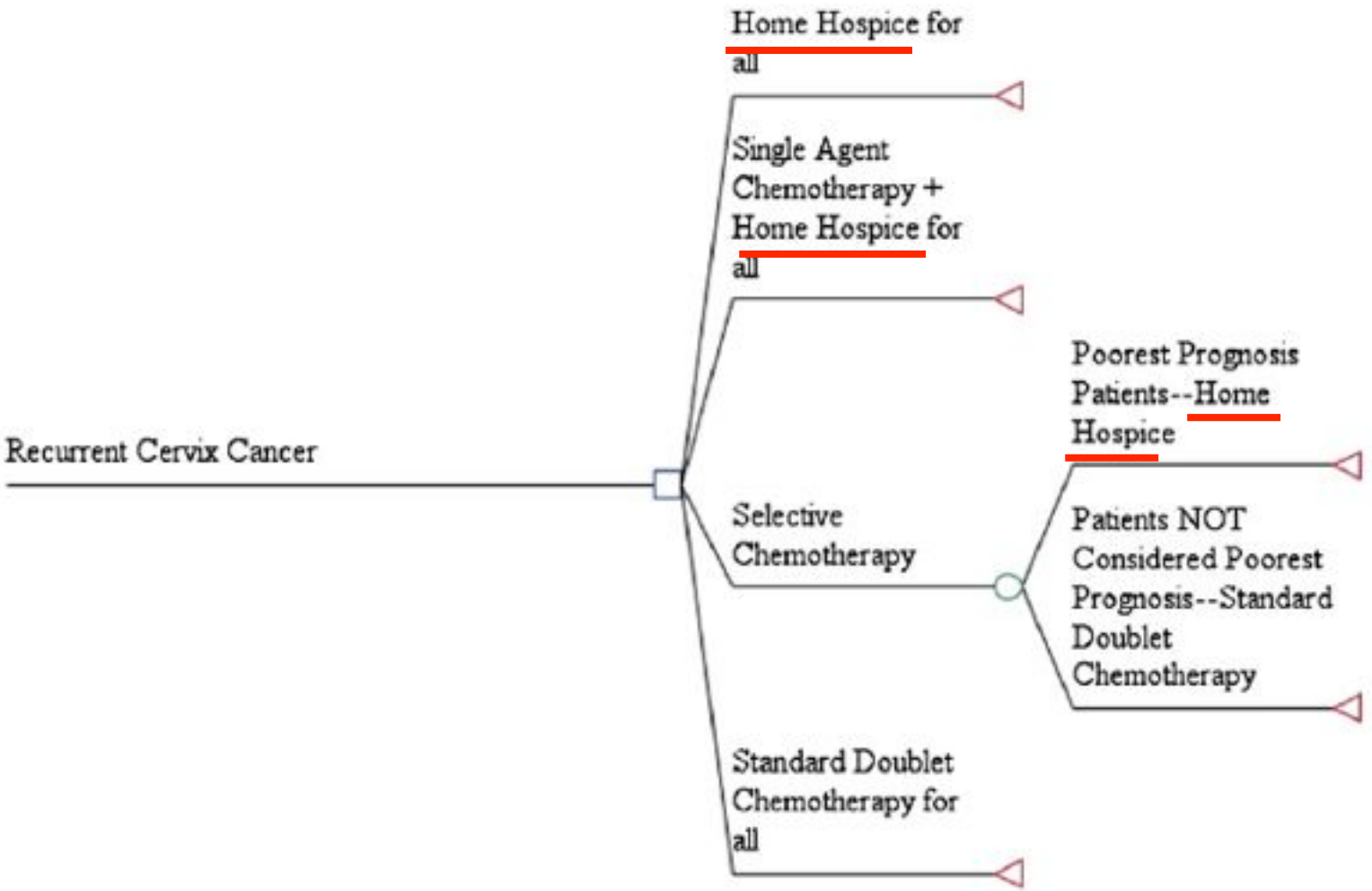
Cost-analysis



Phippen N.T. et al. Gynecol.Oncol. 2013

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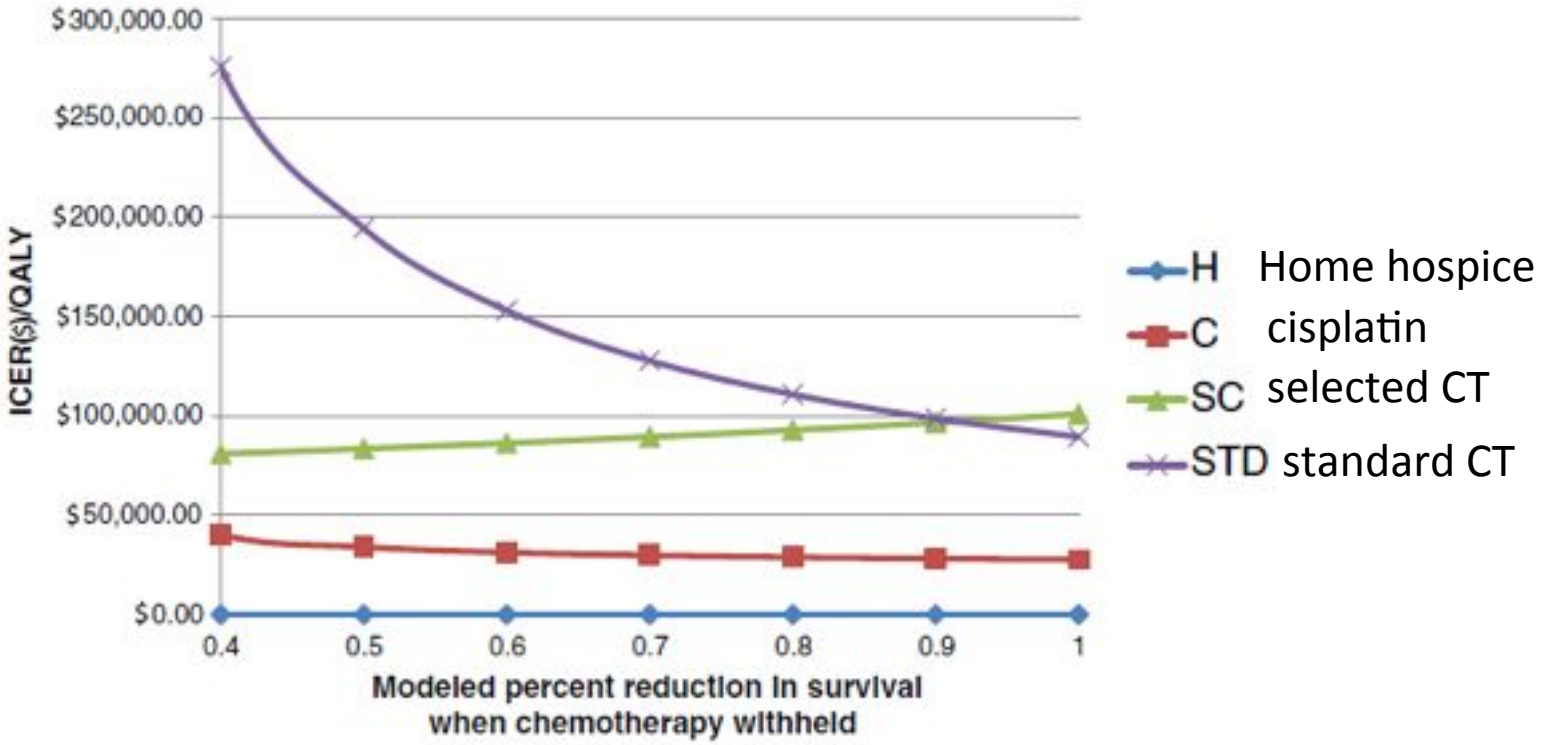
cost-analysis

- survival

Cost-analysis: OS



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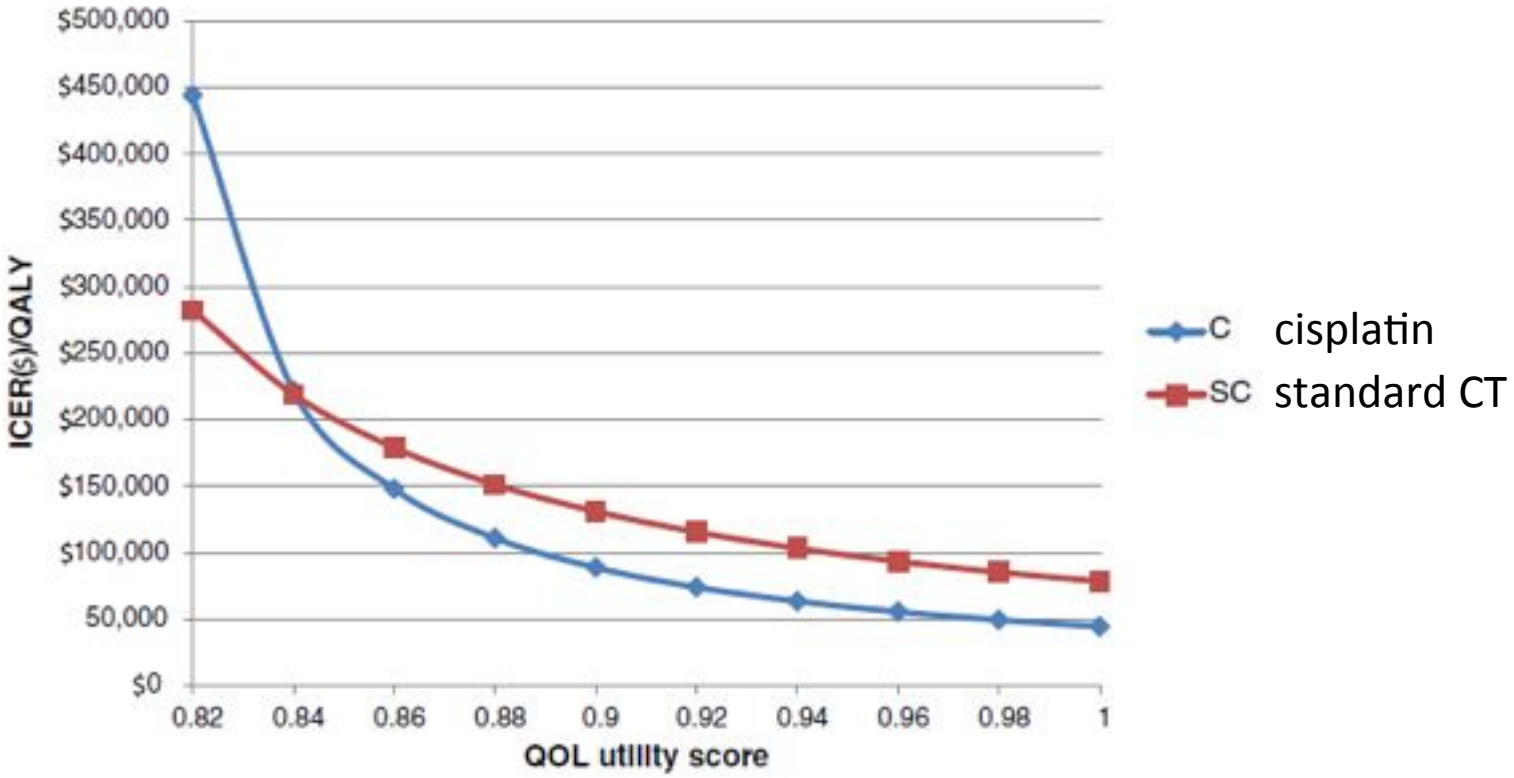
- Survival
- QoL

Cost-analysis: QoL



Phippen N.T. et al. Gynecol.Oncol. 2013

Patients' selection

Poor prognosis pts (4-5 risk factors*):

- **Home Hospice Care +/- single agent CT**

- **-Mid(2-3 RF*)-'Good' prognosis pts (0-1 RF*) :**
  - **doublet chemotherapy +/- bevacizumab**

*** RISK FACTORS**

1) race: black
2) PS: 1-2
3) site of RL: pelvic
4) prior RT-CT
5) time to relapse <1 yr

Phippen N.T. et al. Gynecol.Oncol. 2013

Take-home

- Chemotherapy is a palliative treatment
- CDDP based doublet chemotherapy: most effective
  - CDDP + TAXOL: gold standard
    - CBDCA may sobstitute CDDP
    - Other drugs in combination with CDDP: different toxicity profile
- Bevacizumab + chemotherapy: effective
- Selective treatments according to pg factors
- Home Hospice Care: improves results decreasing costs

Take-home

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