Vienna ESMO, October 2012

Assembling evidence in Rare Cancers

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Standard process of development of an anticancer therapy (‘60s)

- Preclinical studies
- Phase I studies in man
- Phase II trial(s)
- Randomised Clinical Trial(s) of adequate size

EBM Definition

“….integrating individual clinical expertise with the best available external clinical evidence from systematic research”

Sackett DL, et al. "Evidence based medicine: what it is and what it isn't". BMJ 312 (7023): 71–2 (1996) .

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Sackett DL, et al. "Evidence based medicine: what it is and what it isn't". BMJ 312 (7023): 71–2 (1996) .

Assembling evidence

- Systematic search of RCT's addressing the question of interest

- (Assessment of quality)

- Meta-analysis (Synthesis)

Standard process of development of an anticancer therapy (EMB)

- Preclinical studies
- Phase I studies in man
- Phase II trial(s)
- Randomised Clinical Trial(s) of adequate size
- **Systematic Review & Meta-analysis**
- **Clinical Recommendation (Guideline)**

Sources of prior evidence

- *Randomised Trials*
- Biological & Preclinical Studies
- Case-reports
- Uncontrolled studies
- Studies with surrogate endpoints
- Studies on other similar cancers
- Studies on the same cancer in different stages
- Others?

Meta-analyses in frequent tumors

- ***Randomised Trials***
- Biological & Preclinical Studies
- Case-reports
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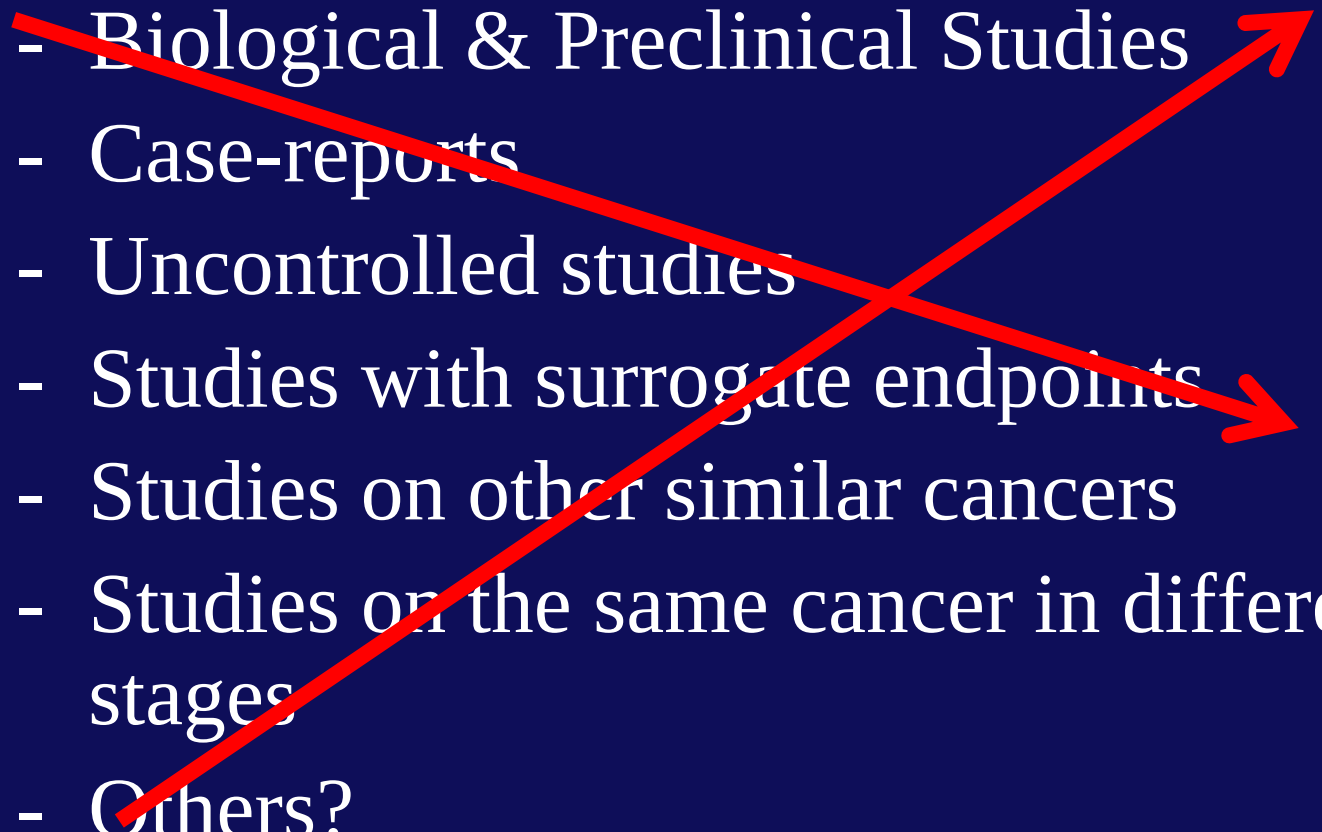
- Others?



Meta-analyses in frequent tumors

- ***Randomised Trials***

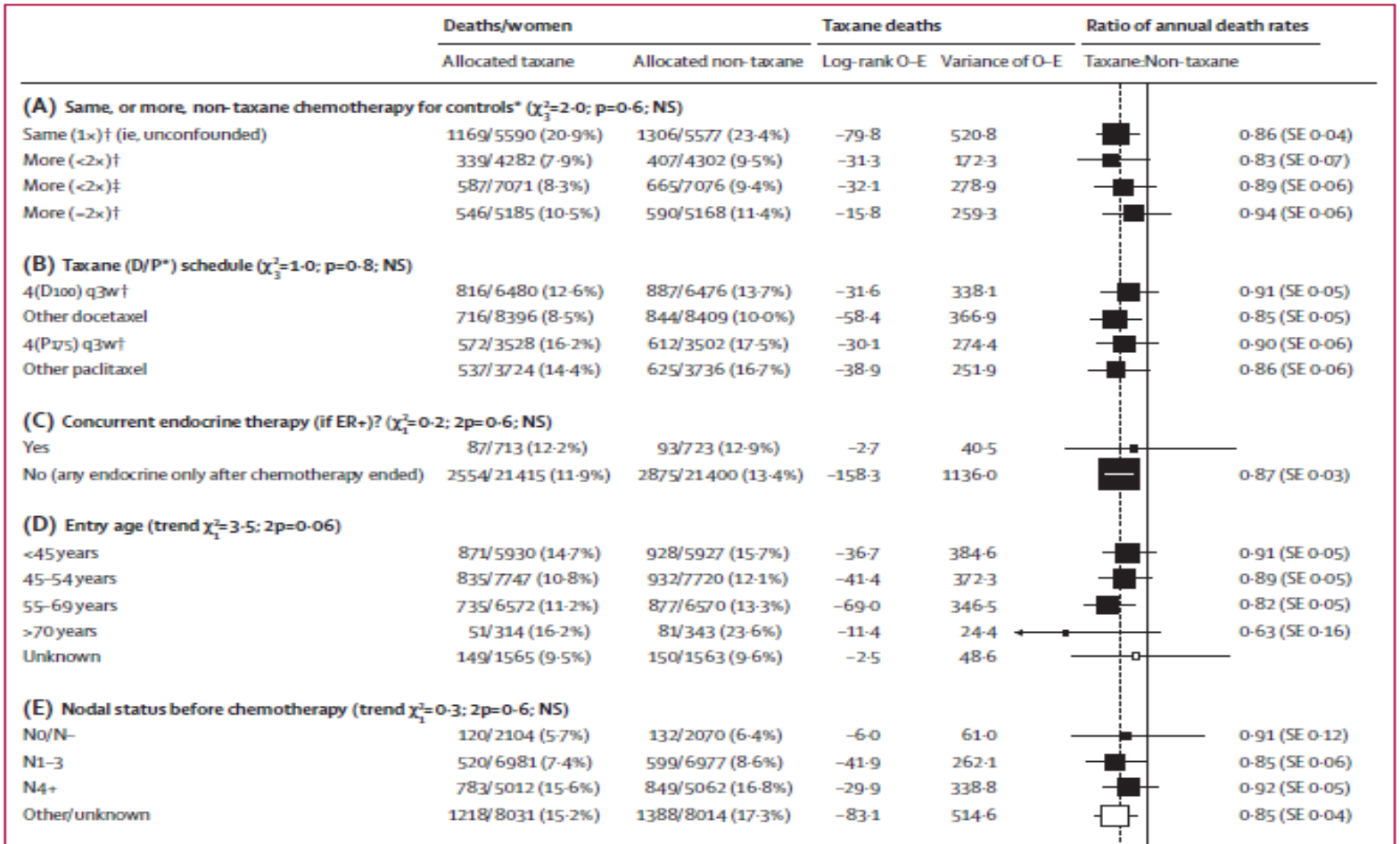
Weighted exclusively based on their size

(*and quality?*)

Early Breast Cancer Trialist Cooperative Group (Oxford, 1985-present)

Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among **100 000 women in 123 randomised trials** (Lancet 2012)

Taxane-plus-anthracycline-based regimens (Tax+anth) versus control with (left) the same or (right) more non-taxane CTX



	Deaths/women		Taxane deaths		Ratio of annual death rates
	Allocated taxane	Allocated non-taxane	Log-rank O–E	Variance of O–E	Taxane:Non-taxane
(A) Same, or more, non-taxane chemotherapy for controls* (χ^2_3=2·0; p=0·6; NS)					
Same (1×)† (ie, unconfounded)	1169/5590 (20·9%)	1306/5577 (23·4%)	−79·8	520·8	0·86 (SE 0·04)
More (<2×)†	339/4282 (7·9%)	407/4302 (9·5%)	−31·3	172·3	0·83 (SE 0·07)
More (<2×)‡	587/7071 (8·3%)	665/7076 (9·4%)	−32·1	278·9	0·89 (SE 0·06)
More (≥2×)†	546/5185 (10·5%)	590/5168 (11·4%)	−15·8	259·3	0·94 (SE 0·06)
(B) Taxane (D/P*) schedule (χ^2_3=1·0; p=0·8; NS)					
4(D100) q3w†	816/6480 (12·6%)	887/6476 (13·7%)	−31·6	338·1	0·91 (SE 0·05)
Other docetaxel	716/8396 (8·5%)	844/8409 (10·0%)	−58·4	366·9	0·85 (SE 0·05)
4(P175) q3w†	572/3528 (16·2%)	612/3502 (17·5%)	−30·1	274·4	0·90 (SE 0·06)
Other paclitaxel	537/3724 (14·4%)	625/3736 (16·7%)	−38·9	251·9	0·86 (SE 0·06)
(C) Concurrent endocrine therapy (if ER+)? (χ^2_1=0·2; 2p=0·6; NS)					
Yes	87/713 (12·2%)	93/723 (12·9%)	−2·7	40·5	
No (any endocrine only after chemotherapy ended)	2554/21415 (11·9%)	2875/21400 (13·4%)	−158·3	1136·0	0·87 (SE 0·03)
(D) Entry age (trend χ^2_1=3·5; 2p=0·06)					
<45 years	871/5930 (14·7%)	928/5927 (15·7%)	−36·7	384·6	0·91 (SE 0·05)
45–54 years	835/7747 (10·8%)	932/7720 (12·1%)	−41·4	372·3	0·89 (SE 0·05)
55–69 years	735/6572 (11·2%)	877/6570 (13·3%)	−69·0	346·5	0·82 (SE 0·05)
≥70 years	51/314 (16·2%)	81/343 (23·6%)	−11·4	24·4	0·63 (SE 0·16)
Unknown	149/1565 (9·5%)	150/1563 (9·6%)	−2·5	48·6	
(E) Nodal status before chemotherapy (trend χ^2_1=0·3; 2p=0·6; NS)					
N0/N–	120/2104 (5·7%)	132/2070 (6·4%)	−6·0	61·0	0·91 (SE 0·12)
N1–3	520/6981 (7·4%)	599/6977 (8·6%)	−41·9	262·1	0·85 (SE 0·06)
N4+	783/5012 (15·6%)	849/5062 (16·8%)	−29·9	338·8	0·92 (SE 0·05)
Other/unknown	1218/8031 (15·2%)	1388/8014 (17·3%)	−83·1	514·6	0·85 (SE 0·04)

NCCN

National Comprehensive Cancer Network

Clinical Practice Guidelines

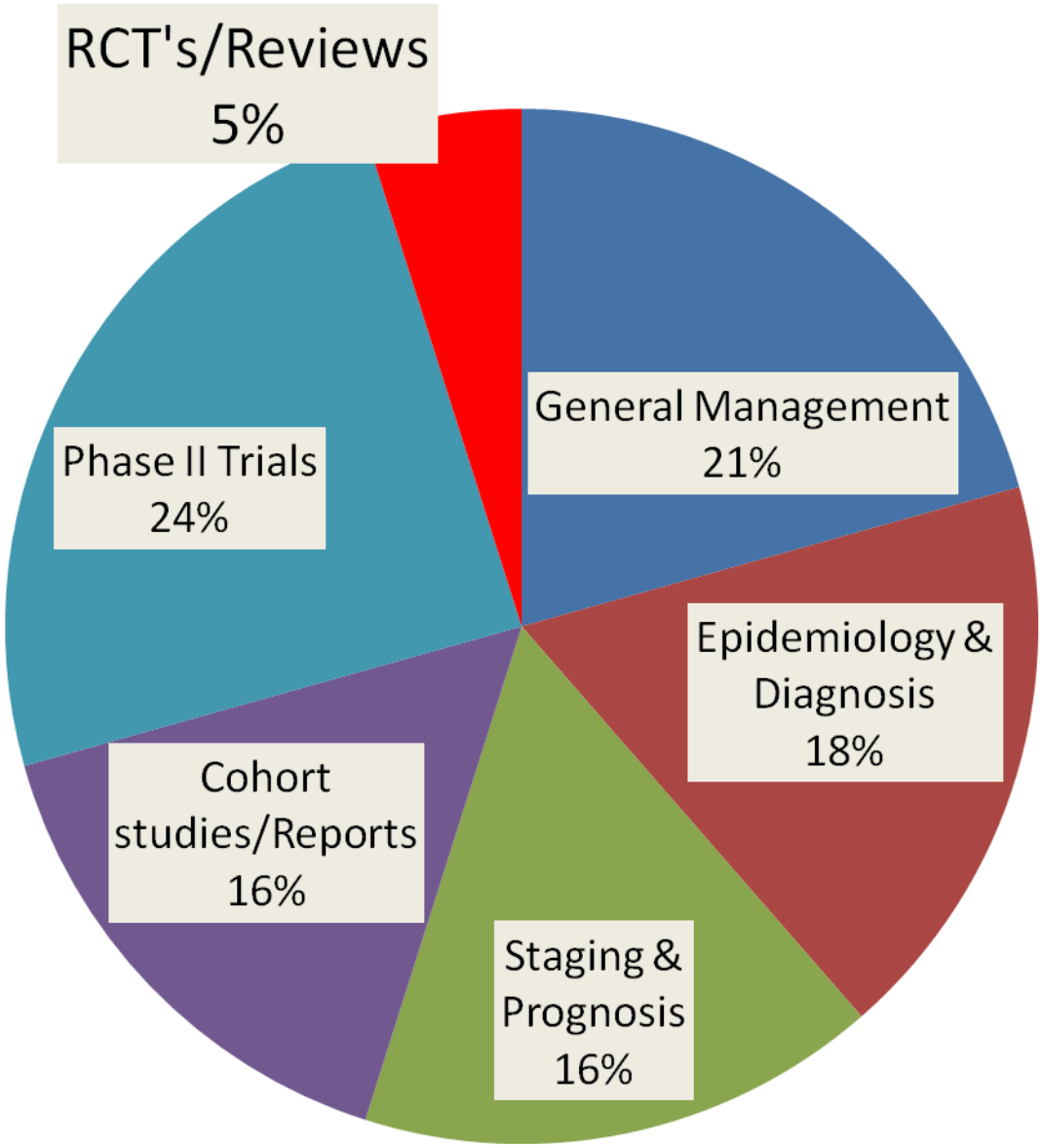
in Oncology

Neuroendocrine Tumors, 2012

References in NCCN Guidelines in Neuroendocrine tumors

Type of Study	Number	
General Management	38 (20%)	Mostly Reviews
Epidemiology & Diagnosis	33 (18%)	Incl. Genetic studies
Staging & Prognosis	30 (16%)	Incl. Consensus papers
Cohort studies	29 (16%)	Mostly case-series
Phase II trials	45 (24%)	Incl. Informal trials (e.g surgery, RXT)
Phase III/SR	9 (5%)	Incl. 1 Syst. Review

Neuroedocrine Tumors



Neuroendocrine, 2012

Grade 2a: All, except

- Grade 1: 0
- Grade 2b: 12 statements
- Grade 3: 4 statements+ same statement repeated 10 times (“*consider chomogranin A”*)

NCCN Categories of Consensus

- Category 1
- Category 2A
- Category 2B
- Category 3

NCCN Categories of Consensus

- Category 1: There is **uniform** NCCN consensus, ... …**based on high-level evidence** (ie, high-powered randomized clinical trials or meta-analyses)

NCCN Categories of Consensus

- *Category 1: There is uniform NCCN consensus, ...*

- Category 2A: The recommendation is based on **lower level evidence** and there is **uniform** NCCN consensus,...
-

NCCN Categories of Consensus

- *Category 1: There is uniform NCCN consensus, ...*

- *Category 2A: There is uniform NCCN consensus,...*

- Category 2B : There is **nonuniform** NCCN consensus (but no major disagreement), ... based on lower level evidence,… A Category 2B designation should signal to the user that more than one approach can be inferred from the existing data

NCCN Categories of Consensus

- *Category 1: There is uniform NCCN consensus, ...*
- *Category 2A: There is uniform NCCN consensus,...*
- *Category 2B : There is nonuniform NCCN consensus (but no major disagreement), ...*
- Category 3: There is **major** NCCN **disagreement** that the recommendation is appropriate

NCCN

National Comprehensive Cancer Network

Clinical Practice Guidelines

in Oncology

SOFT TISSUE SARCOMA

2005

Table of Contents

NCCN Soft Tissue Sarcoma Panel Members

Soft Tissue Sarcoma
- Soft-Tissue Extremity (EXTSARC-1)
- Retroperitoneal (RETSARC-1)
- Intra-abdominal Sarcomas (ABSARC-1)
  - Gastrointestinal Stromal Tumors (GIST-1)
    Principles of Biopsy (GIST-A)
  - Other Intra-abdominal Sarcomas (GISARC-1)
- Desmoid Tumors (DESMSARC-1)

Sarcoma Surgery Principles (SARC-A)

Principles of Chemotherapy (SARC-B)

Guidelines Index

Print the Sarcoma Guideline

For help using these documents, please click here

Staging

Manuscript

References

Clinical Trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Consensus

Sarcomas NCCN Guidelines 2005

Categories of Consensus:

3: 1 recommendation

2B: 7 recommendations

1: 1 recommendation (STS of the extremities)

- Radiotherapy for Stage I T2a,b low grade

(Chemotherapy as primary treatment when unresectable: no longer 1)

ALL OTHER RECOMMENDATIONS ARE 2A!

2011

Sarcomas NCCN Guidelines 2011

Categories of Consensus:

3: 0 recommendation

2B: 12 recommendations

1: 1 recommendation (STS of the extremities)

For stage IB; final margins <1.0 cm pathway:

"RT (category 1)" changed to "Consider RT (category 1)"

ALL OTHER RECOMMENDATIONS ARE 2A!

Sarcomas NCCN Guidelines 2005 - 2011

Categories of Consensus:

Grade	Number of recommendations	
	2005	2011
1:	1	1
2B:	7	12
3:	1	0

ALL OTHER RECOMMENDATIONS ARE 2A!

ALL OTHER RECOMMENDATIONS ARE 2A

Category 2A: there is **uniform consensus** ….

Lower level evidence is interpreted broadly, …

from phase II or large cohort studies to **individual practitioner experience**.

..in many instances, **the retrospective studies are derived from clinical experience of treating large numbers of patients at a member institution, …**

Inevitably, some recommendations must address clinical situations for which limited or no data exist.

In these instances the congruence of experience-based opinions provide an informed if not confirmed direction for optimizing patient care. .....

Soft Tissue Sarcomas, 2012

All Grade 2a except:

Grade 1: 1 (*Imatinib in pts with completely resected GIST with significant risk of recurrence*)

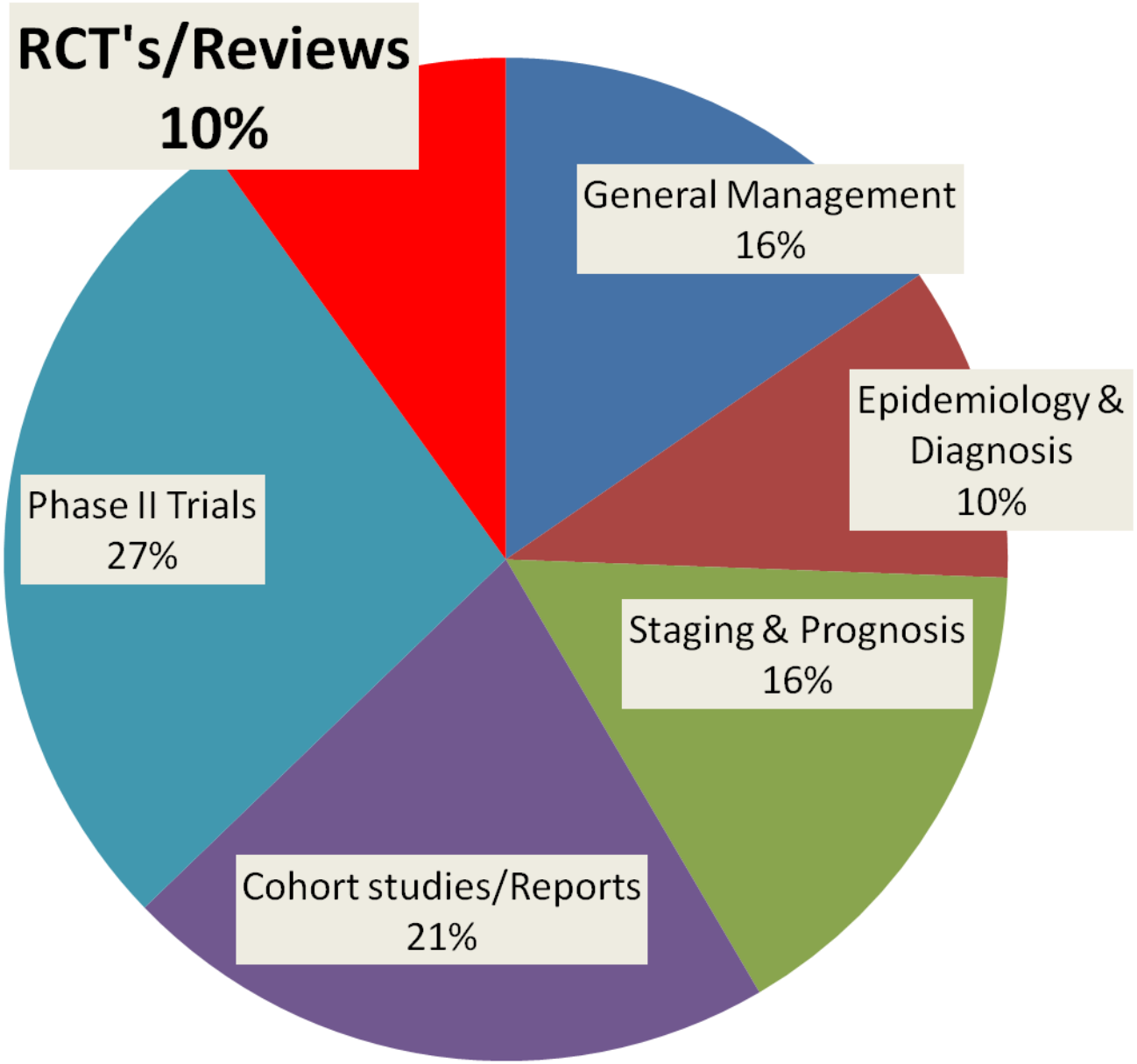
Grade 2b: 7 (with repetitions)

Grade 3: 0

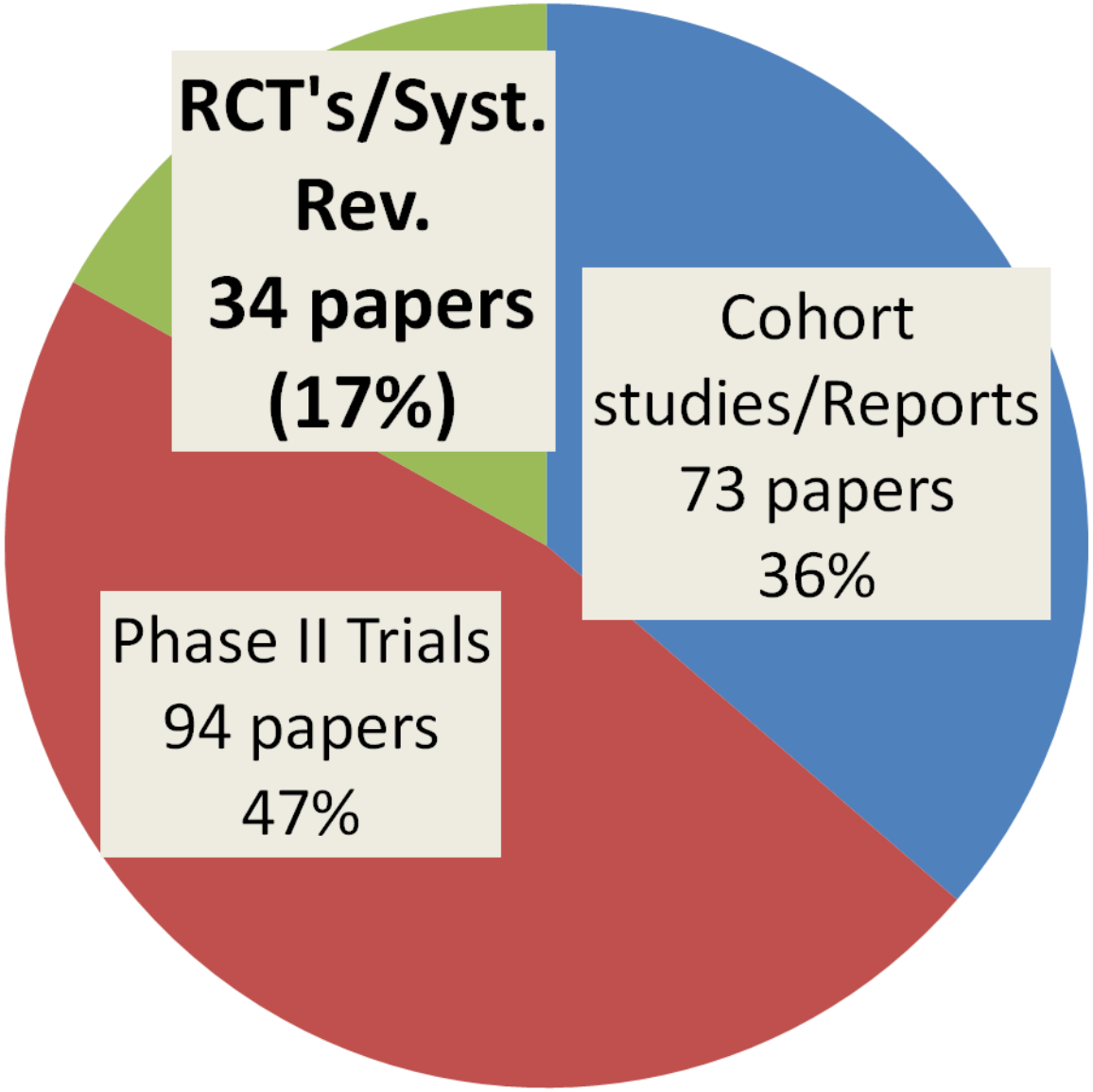
References in NCCCN Guidelines in Soft Tissue Sarcomas (Discussion)

Type of Study	Number	
General Management	53 (15%)	Mostly Reviews
Epidemiology & Diagnosis	35 (10%)	Incl. Genetic studies
Staging & Prognosis	55 (16%)	Incl. Consensus papers
Cohort studies/reports	73 (21%)	Mostly case-series
Phase II trials	94 (27%)	Incl. Informal trials (e.g surgery, RXT)
Phase III/SR	34 (10%)	Incl. a Syst. Review

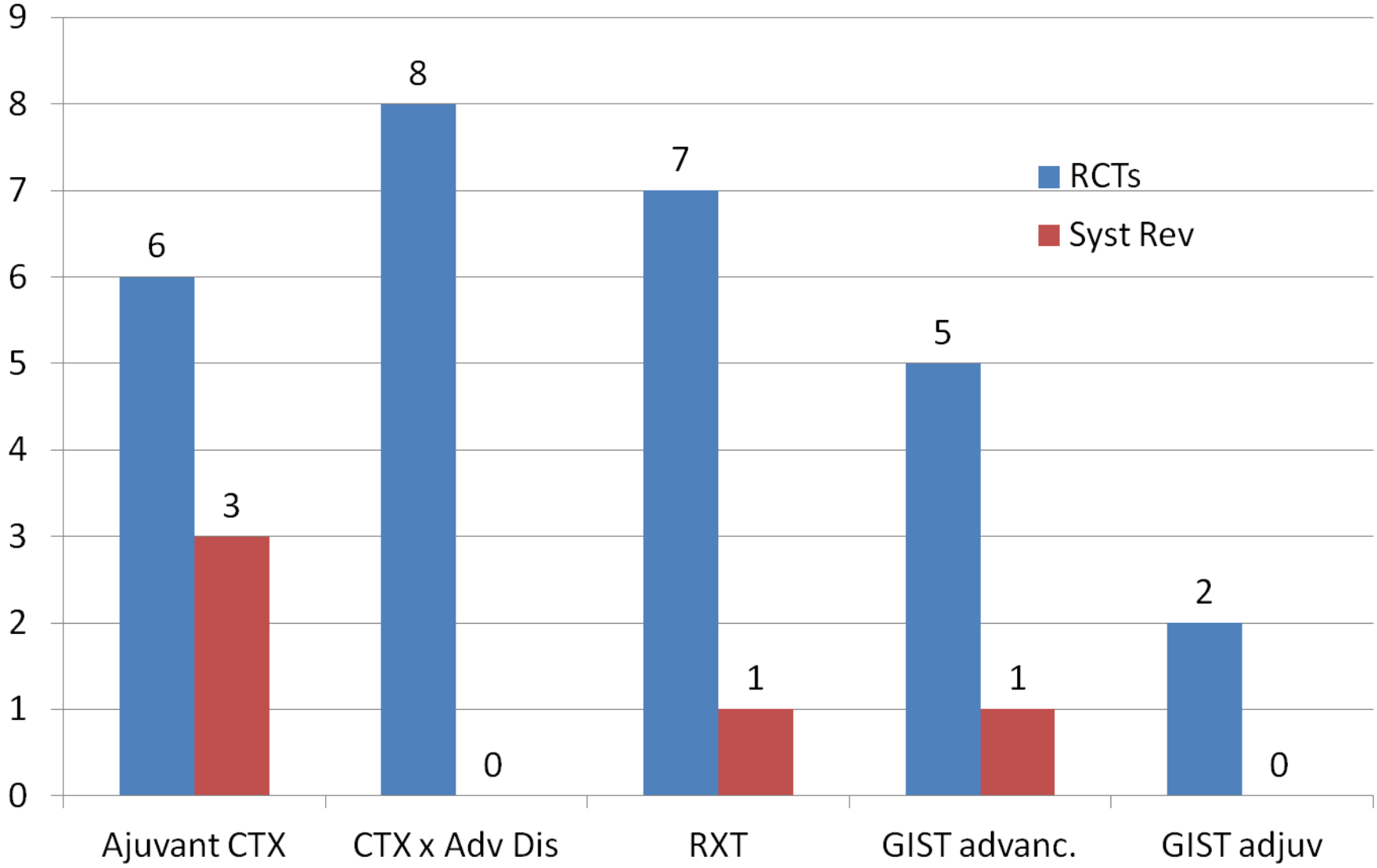
Soft Tissue Sarcomas (Ref.)



Soft Tissue Sarcomas (Therapeutic st.)



Topic of RCTs & S.R in STS's



RCT's and Systematic Reviews cited in NCCCN Guidelines in STS

Topic		Studies (Cit.)	Notes
Adjuv. CTX	RCT	6(6)	All CTX vs no treat.
	Syst Rev.	3(3)	All CTX vs no treat
CTX for Adv Dis	RCT	8(8)	8 different contrasts Doxo Contr. Tx. in 4 st.
RTX	RCT & SR	5(9)	4 cit.ns from 1 study (1 SR)
GIST adv		4(7)	Only sunitinib vs no th. 1 SR on doses
GIST Adjuvant		2	Gleevec vs nil & 1 vs 3 yrs

Only G1 recommendation

Available Evidence on treatments for Rare Tumors

- Case Reports
- Uncontrolled (Phase II?) Trials
- Low quality trials (protocol, selection criteria, assessment of endpoints, exclusions, GCP, etc.)
- **Small Studies**

LOW QUALITY EVIDENCE

Available Evidence on treatments for Rare Tumors

LOW QUALITY EVIDENCE

CLINICAL GUIDELINES?

Available Evidence on treatments for Rare Tumors

LOW QUALITY EVIDENCE

CLINICAL GUIDELINES?

CLINICAL DECISION?

Available Evidence on treatments for Rare Tumors

LOW QUALITY EVIDENCE

CLINICAL GUIDELINES?

CLINICAL DECISION?

Yet, most recommendations are 2A
(Uniform consensus)

Low level of evidence

Vs

High level of agreement

WHY?

WHY?

…because physicians are smarter than they pretend to be…

…and make full use of all the avaialble information!

EBM Definition

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Meta-analyses in frequent tumors

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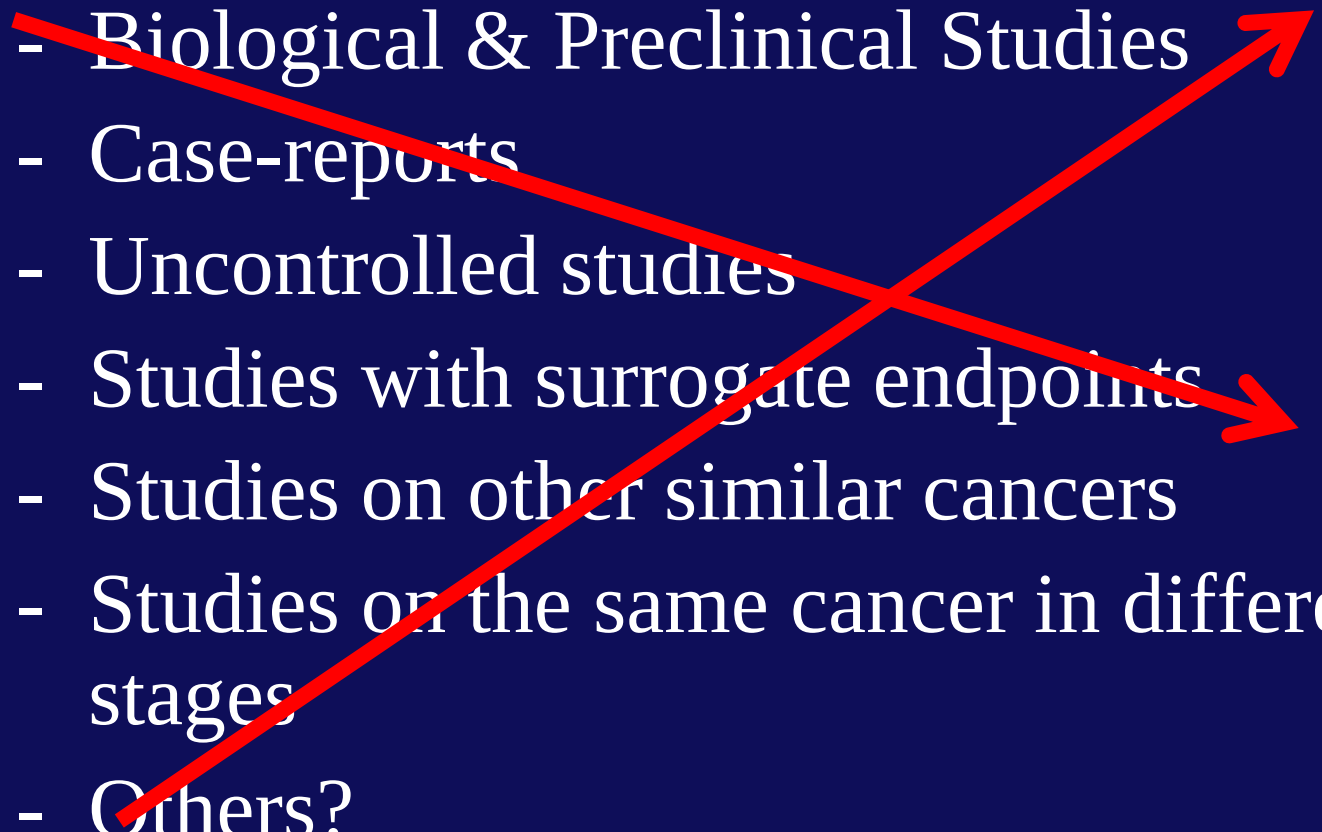


Meta-analyses in frequent tumors

- ***Randomised Trials***

Weighted exclusively based on their size

Best Available Evidence in rare cancers

Often no information/evidence from RCTs focused on the question of interest

- **Studies of questionable validity**
- **Indirect(ly pertinent) evidence**
- *(Pubblication bias?)*

Rare Tumors

- ~~***Randomised Trials***~~
- Biological & Preclinical Studies
- Case-reports
- **Uncontrolled studies**
- **Studies with surrogate endpoints**
- **Studies on other similar cancers**
- **Studies on the same cancer in different stages**
- Others?

EBM in rare cancers

Need to use information from studies

less than 100% VALID ,

less than 100% PERTINENT TO THE QUESTION OF INTEREST,

i.e. (Different cancers, treatments, endpoints)

Clinical Oncology 24 (2012) 294–308

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Radionuclide Therapy in Neuroendocrine Tumours: A Systematic Review

K.Y. Gulenchyn *, X. Yao †, S.L. Asa ‡, S. Singh §, C. Law ||

- No randomised trials
- Only phase II trials with historical comparisons

Systematic Review of Radionucleide therapy in NET (2012)

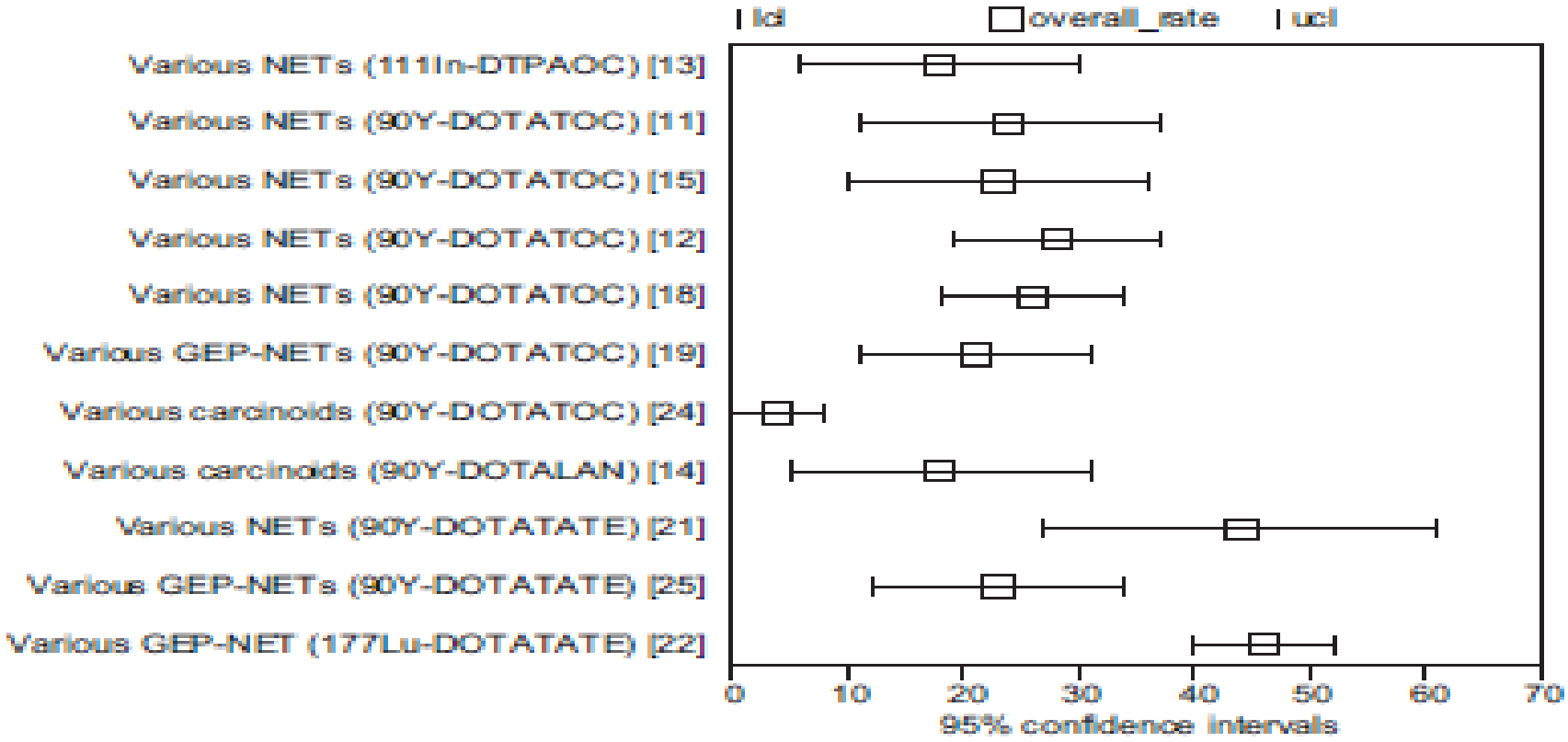


Fig 2. Overall response rates (defined as the sum of the complete response, partial response and minor response rates) with 95% confidence intervals by different peptide receptor radionuclide therapy (PRRT). Lcl, lower confidence interval; ucl, upper confidence

Conclusions (1)

- … peptide receptor radionuclide therapy **seems to be an acceptable option** and is relatively safe in adult advanced NET pts with receptor uptake positive on scintigraphy, but pts renal function must be monitored.
- 131I-MIBG **may be effective** for malignant neuroblastoma, paraganglioma or pheochromocytoma, but its side-effects need to be considered

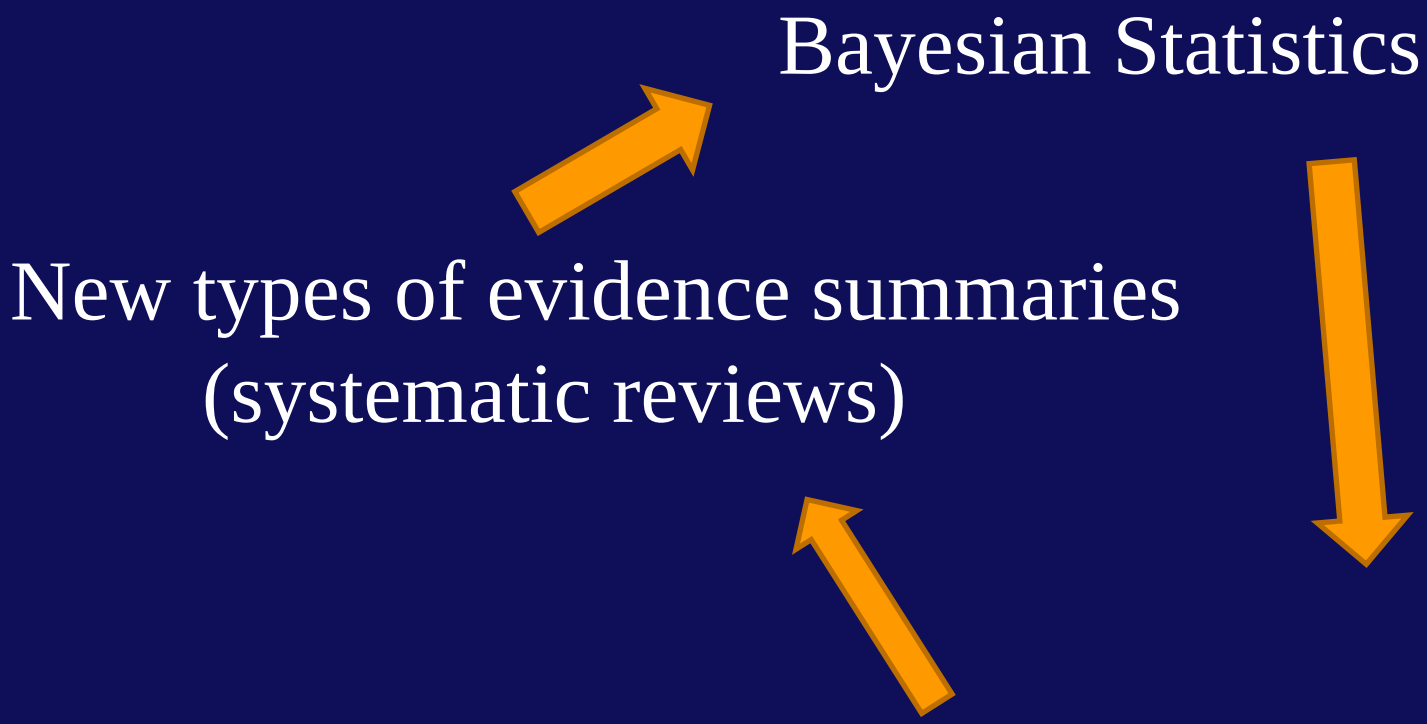
Conclusions (2)

- **No strong evidence exists** to support that one therapeutic radiopharmaceutical is more effective than others.
- **Well-designed and good-quality randomised controlled trials are required on this research topic**

Recent statistical developments (<10 yrs) in rare cancers

- Bayesian Statistics
- New types of systematic reviews
- Adaptive trials

Recent developments (<10 yrs) in rare cancers



Recent developments (<10 yrs) in rare cancers

Systematic Reviews in rare cancers

Need to use information from studies

- less than 100% VALID
- less than 100% PERTINENT TO THE QUESTION OF INTEREST,

Weighted on the basis of their quality and pertinence

Proposal

Tan SB, Dear KB, Bruzzi P, Machin D. Strategy for randomised clinical trials in rare cancers. BMJ. 2003 Jul 5;327(7405**):47-9.**

- Each piece of information (study) has to be used, weighted according to its:
  - Precision (size)
  - Quality
  - **Pertinence (relevance to the study question)**

PERTINENCE ?

- CANCER
- TREATMENT CONTRAST
- ENDPOINT
- **Arbitrary but explicit weights**

Differences between the present and the proposed approach

- Present :
  - Rational but informal integration of the available knowledge (NCCN 2A)

  Problems

  - Lack of transparency
  - No quantitative estimates of benefits/arms

Differences between the present and the proposed approach

- *Present :*
  - *Rational but informal integration of the available knowledge (NCCN 2A)*
- Proposed
  - Formal, explicit and quantitative integration of the available knowledge
    - Verifiable quantitative methods
    - Sensitivity analyses
    - Focus on summary effect estimates

Example

- Vemurafenib in BRAF+ **pediatric** melanoma

Example

- Vemurafenib in BRAF+ **pediatric** melanoma

Available Evidence:

- RCT in adults: completed, positive

+

- Uncontrolled trial in children: ongoing; if improvement over historical controls

= NCCN 2A

Example: New Approach

- Vemurafenib in BRAF+ **pediatric** melanoma

Available Evidence:

1. RCT in adults (completed, positive, indirect)

+

2. Uncontrolled trial in children (ongoing)

Pertinent but invalid

Example: new approach

- Vemurafenib in BRAF+ **pediatric** melanoma

Available Evidence

1. RCT in adults:

HR = 0.5, improvement in median OS = 2 mo.s

Indirect evidence (pertinence 80%?)

Validity = 100%

Weight = 80%

Example: new approach

- Vemurafenib in BRAF+ **pediatric** melanoma

Available Evidence:

2. Uncontrolled trial in children (comparison historical controls)

Validity: 40% (bias toward stronger effect)

Pertinence: 100%

Weight = 40% (+ bias: 30%)

If observed HR = 0.8

Meta-analysis

Study	HR	Weight
RCT in adults	0.5	0.8
	+	
Trial in children	0.8(x1.3)=0.94	0.4

(less effective in children)

Weighted Average = (0.5w1+0.94w2)/(w1+w2)
= 0.7 = Best estimate of risk reduction in children (-30%)

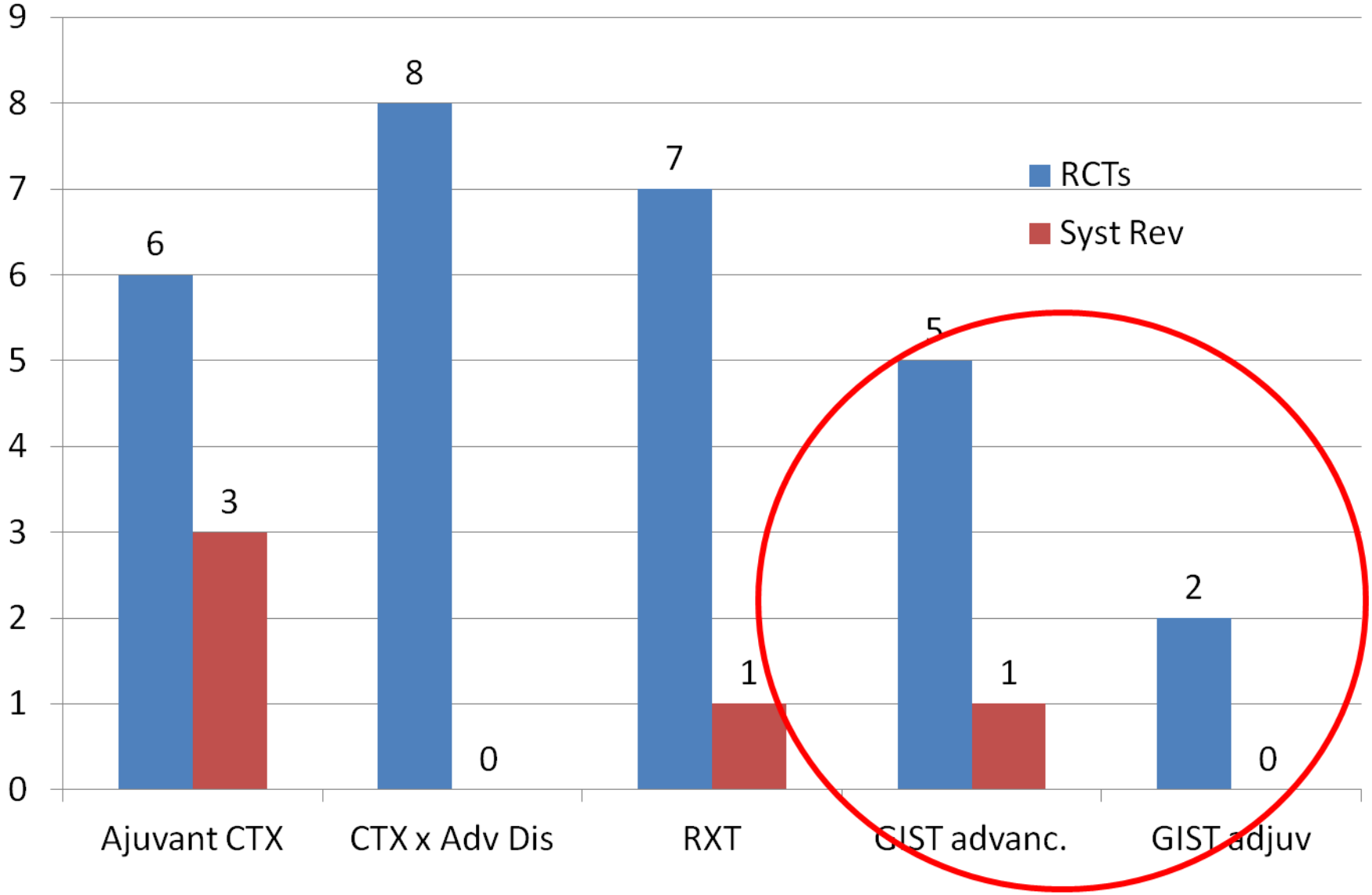
Assembling evidence in rare cancers

Need to develop and validate new (meta-analytic) approaches to summarize prior information in rare tumors

Requirements

- Explicit
- Quantitative
- Reproducible

Topic of RCTs & S.R in STS's



New generation of efficacy trials in rare cancers (from 2000 on…)

- Uncontrolled efficacy (phase III) trials of high quality
- Randomized activity (Phase II) trials followed by uncontrolled efficacy trials (with historical controls)
- RCT's with surrogate endpoints
- Adaptive, Bayesian, activity/efficacy RCT's
- **Unconventional Systematic Reviews?**