How to critically evaluate scientific publications

Residents/CE day
ECVP/ECVCP/ESVP/ESVCP 2019

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Why reading articles?

Because we want to stay up-to-date and perform veterinary medicine according to EBVM

What is EBVM?

"**Evidence Based Veterinary Medicine** is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients."

"The practice of EBVM means integrating individual clinical expertise with the best available external clinical evidence […]"

(Sackett et all, 2000)

What does EBVM mean in daily practice?

- Consciously reflect on the basis of the decisions you make in practice
- Deliberately weighing up evidence from the literature, own clinical expertise and the wishes of the owner(s)

How to perform EBVM?

Roadplan

1. Formulate specific questions that can be looked up
2. Search in literature (especially via online databases)
3. Judge literature (source, methodology, reasoning, conclusions)
4. Integrate findings from literature
5. Evaluate results

Formulate specific questions

- Make specific questions that can be looked up:
  - PICO
    - Patient/Population/Problem
    - Intervention
    - Comparison
    - Outcome
  - Can be related to diagnosis, treatment, prognosis, prevention

Example

- Dog with splenic hemangiosarcoma
- Owner wants to know if something else after surgery can be done

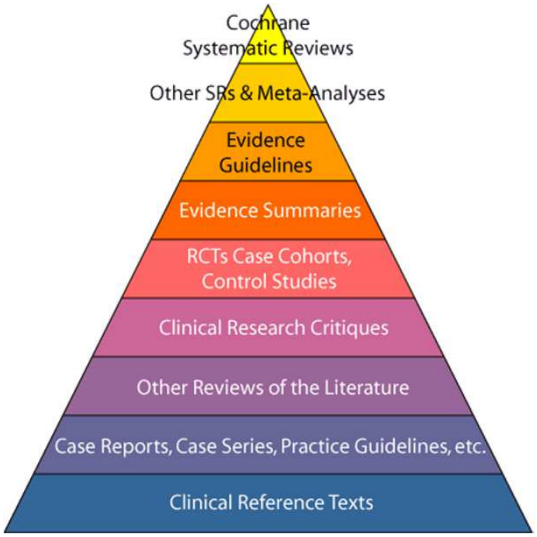
Example

- PICO
  - Patient/ Population/Problem
    - Dogs with splenic hemangiosarcoma
  - Intervention
    - Surgery with adjuvant therapy
  - Comparison
    - Surgery alone
  - Outcome
    - Do they have a longer overall survival?

Search in literature

- What is more reliable?
  - Text books or case reports in refereed journals?
  - Congress research abstracts or case reports in refereed journals?

Evaluation of literature



Cochrane Review

- A Cochrane Review is a scientific investigation in itself, with a pre-planned methods section and an assembly of original studies (predominantly randomised controlled trials and clinical controlled trials, but also sometimes, non-randomised observational studies) as their 'subjects'. The results of these multiple primary investigations are synthesized by using strategies that limit bias and random error. These strategies include a comprehensive search of all potentially relevant studies and the use of explicit, reproducible criteria in the selection of studies for review. Primary research designs and study characteristics are appraised, data synthesized, and results interpreted.

Abstract

Jump to...

Background

High-dose chemotherapy with autologous stem cell support (HDT) has been proven effective in relapsed aggressive non-Hodgkin lymphoma (NHL). However, conflicting results of HDT as part of first-line treatment have been reported in randomised controlled trials (RCTs). We undertook a systematic review and meta-analysis to assess the effects of such treatment.

Objectives

To determine whether high-dose chemotherapy with autologous stem cell transplantation as part of first-line treatment improves survival in patients with aggressive non-Hodgkin lymphoma.

Search methods

MEDLINE, EMBASE, Cancer Lit, the Cochrane Library and smaller databases, Internet-databases of ongoing trials, conference proceedings of the American Society of Clinical Oncology and the American Society of Hematology were searched until September 2006. An update search in MEDLINE and CENTRAL was done in June 2010, no more trials fulfilling the inclusion criteria were identified. We included full-text, abstract publications and unpublished data.

Selection criteria

Randomised controlled trials comparing conventional chemotherapy versus high-dose chemotherapy in the first-line treatment of adults with aggressive non-Hodgkin lymphoma were included in this review.

Data collection and analysis

Eligibility and quality assessment, data extraction and analysis were done in duplicate. All authors were contacted to obtain missing data and asked to provide individual patient data.

Main results

Fifteen RCTs including 3079 patients were eligible for this meta-analysis. Overall treatment-related mortality was 6.0% in the HDT group and not significantly different compared to conventional chemotherapy (OR 1.33 [95% CI 0.91 to 1.93], P = 0.14). 13 studies including 2018 patients showed significantly higher CR rates in the group receiving HDT (OR 1.32, [95% CI 1.09 to 1.59], P = 0.004). However, HDT did not have an effect on OS, when compared to conventional chemotherapy. The pooled HR was 1.04 ([95% CI 0.91 to 1.18], P = 0.58). There was no statistical heterogeneity among the trials. Sensitivity analyses underlined the robustness of these results. Subgroup analysis of prognostic groups according to IPI did not show any survival difference between HDT and controls in 12 trials (low and low-intermediate risk IPI: HR 1.41[95% CI 0.95 to 2.10], P = 0.09; high-intermediate and high risk IPI: HR 0.97 [95% CI 0.83 to 1.13], P = 0.71. Event-free survival (EFS) also showed no significant difference between HDT and CT (HR 0.93, [95% CI 0.81 to 1.07], P = 0.31). Other possible risk factors such as the proportion of patient with diffuse large cell lymphoma, protocol adherence, HDT strategy, response status before HDT, conditioning regimens and methodological issues were analysed in sensitivity analyses. However, there was no evidence for an association between these factors and the results of our analyses.

Authors' conclusions

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Despite higher CR rates, there is no benefit for high-dose chemotherapy with stem cell transplantation as a first line treatment in patients with aggressive NHL.

However, in veterinary medicine no Cochrane Review available

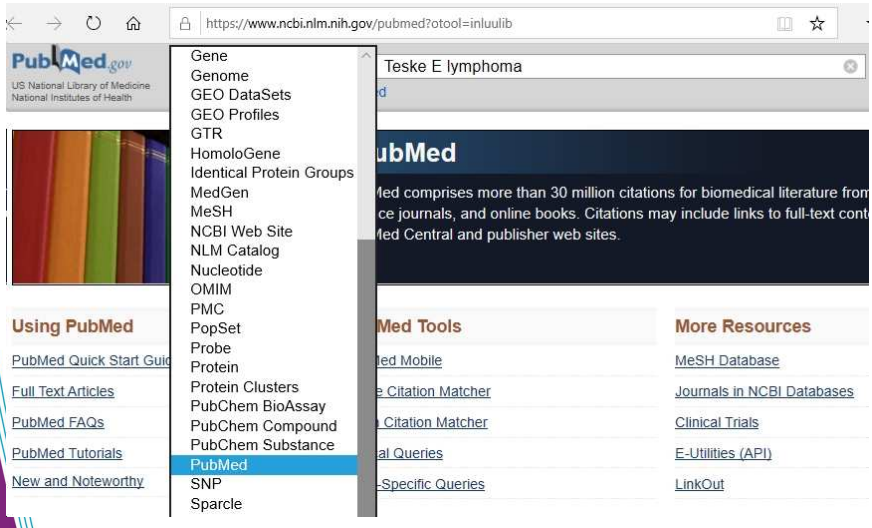
Searching the literature and selecting the right references

Databases and basics of literature search

- Medical library resources
- Review articles
- Databases of medical literature
  - Medline/PubMed, Scopus
  - Full-text databases
  - Electronic journals

MEDLINE:

- Bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the health care system, and the preclinical sciences.
- Contains bibliographic citations and author abstracts from more than 5,200 biomedical journals published in the United States and 70 other countries.
- The database contains over 25 million citations dating back to the mid-1960s
- Coverage is worldwide, but most records are from English-language sources or have English abstracts



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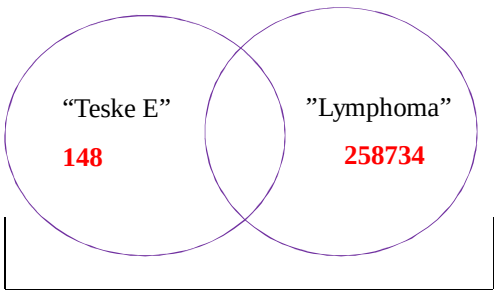
Keywords

- Major concepts or variables of a research problem or topic used to search a database
- May be single terms or phrase
- Can also be author
- Each keyword used should be listed in a written search plan

Search strategies



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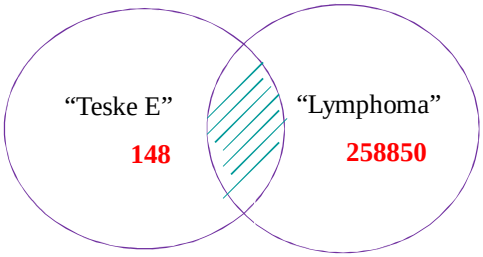

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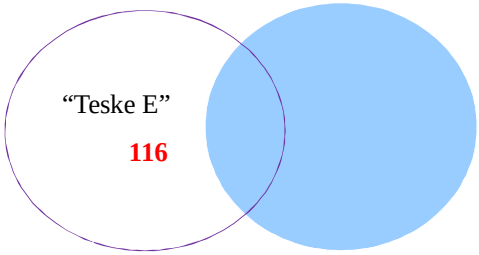
Search strategies



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Suenaga M et al. Vet J. (2017)
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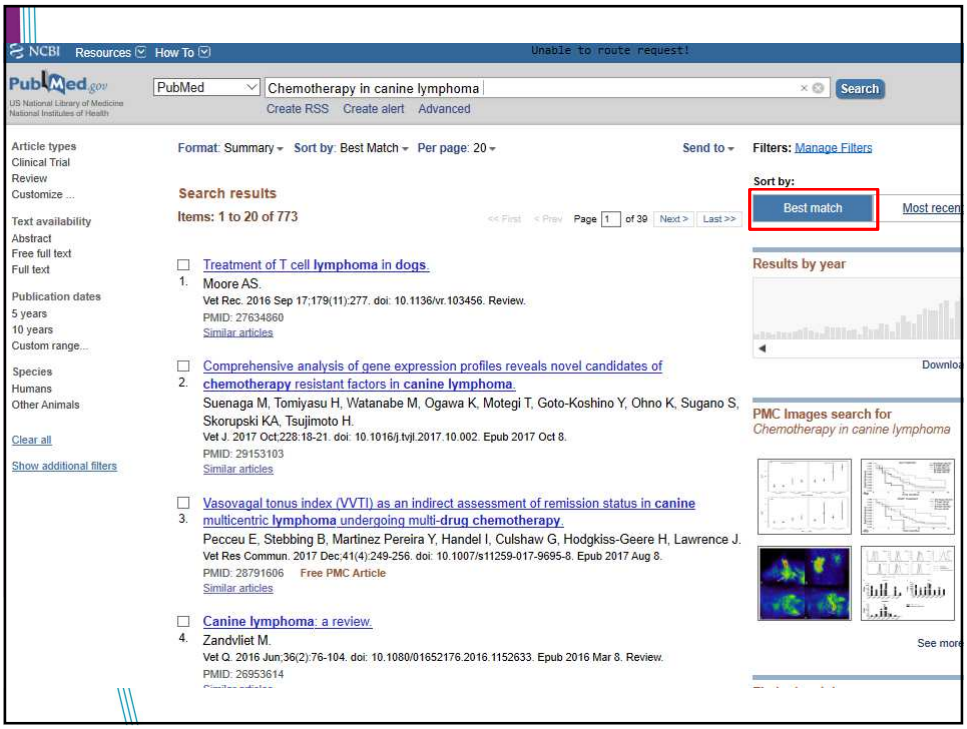
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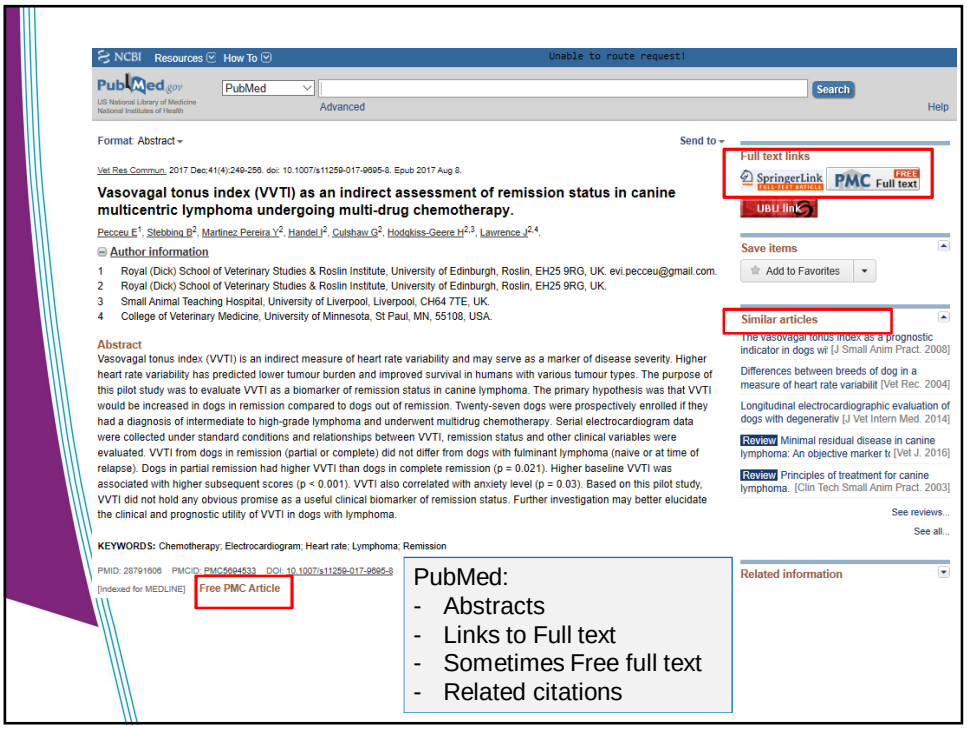
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Vasovagal tonus index (VVTI) as an indirect assessment of remission status in canine multicentric lymphoma undergoing multi-drug chemotherapy.
Pecceu E[1], Stebbing B[2], Martinez Pereira Y[2], Handel I[2], Culshaw G[2], Hodgkiss-Geere H[2,3], Lawrence J[2,4].
Author information
1 Royal (Dick) School of Veterinary Studies & Roslin Institute, University of Edinburgh, Roslin, EH25 9RG, UK. evi.pecceu@gmail.com.
2 Royal (Dick) School of Veterinary Studies & Roslin Institute, University of Edinburgh, Roslin, EH25 9RG, UK.
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4 College of Veterinary Medicine, University of Minnesota, St Paul, MN, 55108, USA.
Abstract
Vasovagal tonus index (VVTI) is an indirect measure of heart rate variability and may serve as a marker of disease severity. Higher heart rate variability has predicted lower tumour burden and improved survival in humans with various tumour types. The purpose of this pilot study was to evaluate VVTI as a biomarker of remission status in canine lymphoma. The primary hypothesis was that VVTI would be increased in dogs in remission compared to dogs out of remission. Twenty-seven dogs were prospectively enrolled if they had a diagnosis of intermediate to high-grade lymphoma and underwent multidrug chemotherapy. Serial electrocardiogram data were collected under standard conditions and relationships between VVTI, remission status and other clinical variables were evaluated. VVTI from dogs in remission (partial or complete) did not differ from dogs with fulminant lymphoma (naive or at time of relapse). Dogs in partial remission had higher VVTI than dogs in complete remission (p = 0.021). Higher baseline VVTI was associated with higher subsequent scores (p < 0.001). VVTI also correlated with anxiety level (p = 0.03). Based on this pilot study, VVTI did not hold any obvious promise as a useful clinical biomarker of remission status. Further investigation may better elucidate the clinical and prognostic utility of VVTI in dogs with lymphoma.
KEYWORDS: Chemotherapy; Electrocardiogram; Heart rate; Lymphoma; Remission
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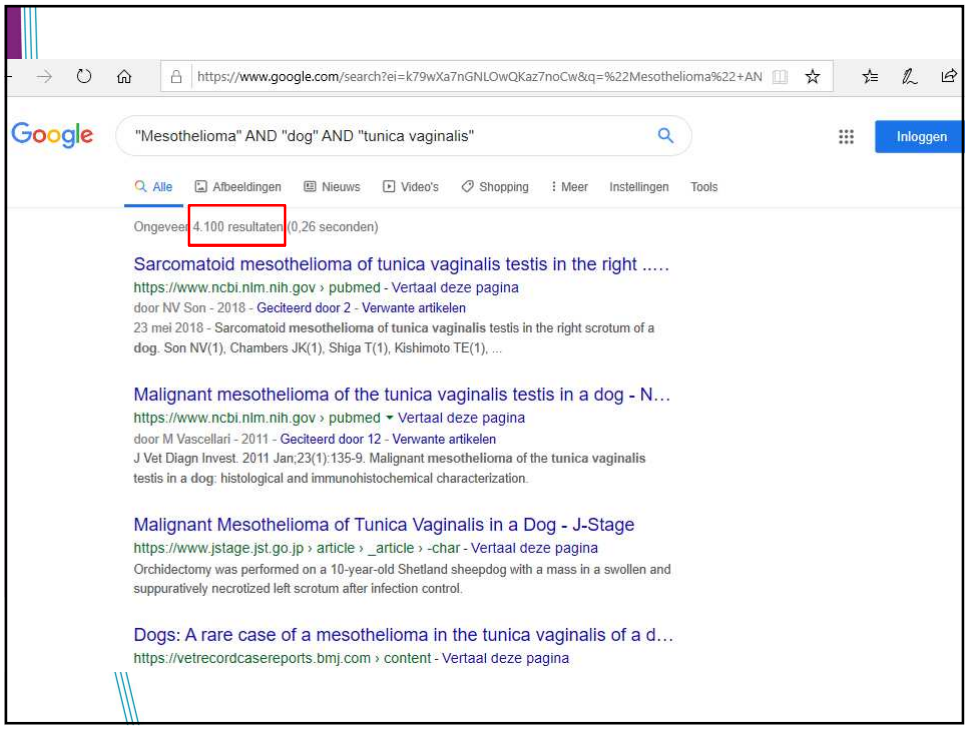
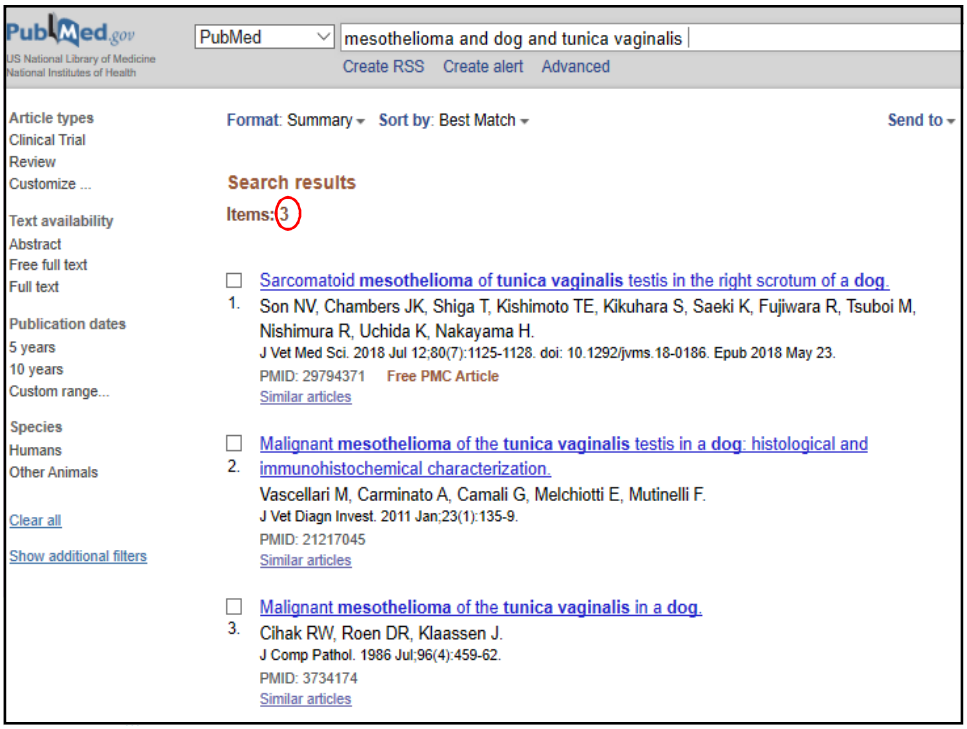
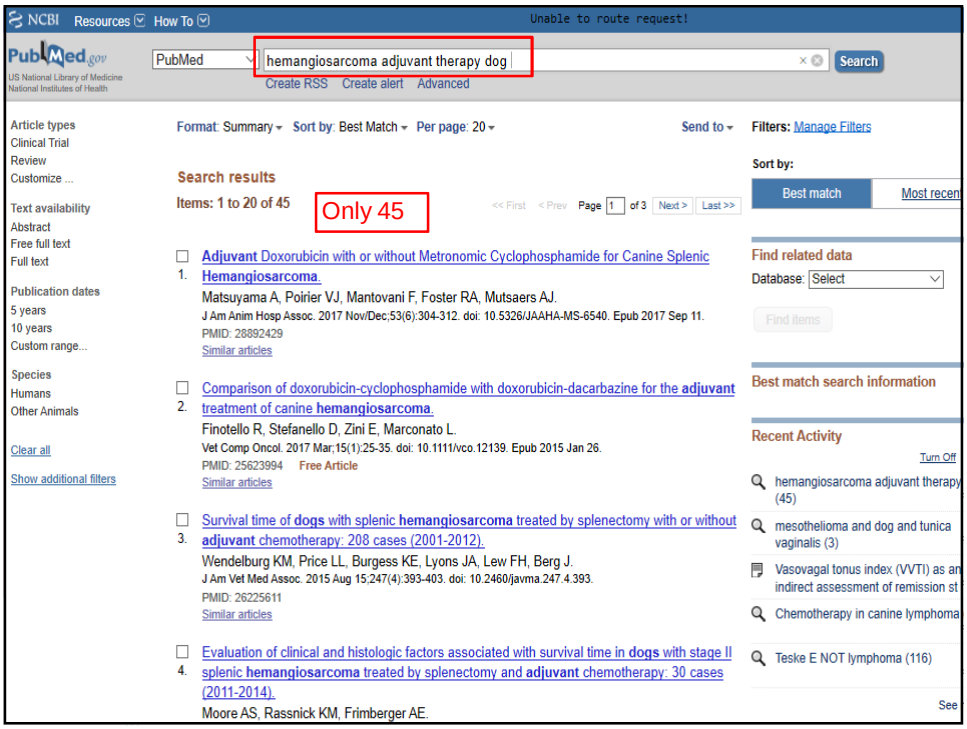




Search terms

- Sometimes better not to be too explicit (many search terms)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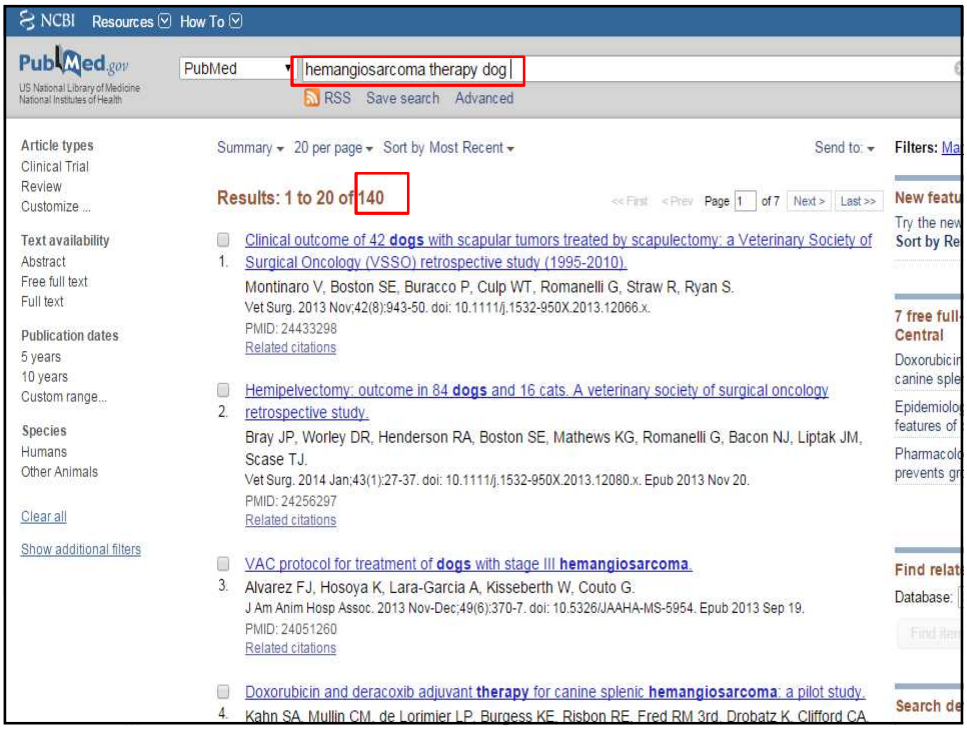
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Bray JP, Worley DR, Henderson RA, Boston SE, Mathews KG, Romanelli G, Bacon NJ, Liptak JM, Scase TJ.
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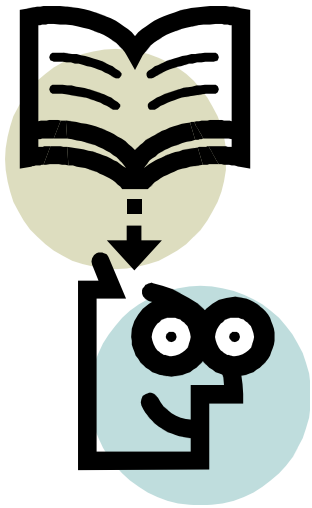


What kind of paper?

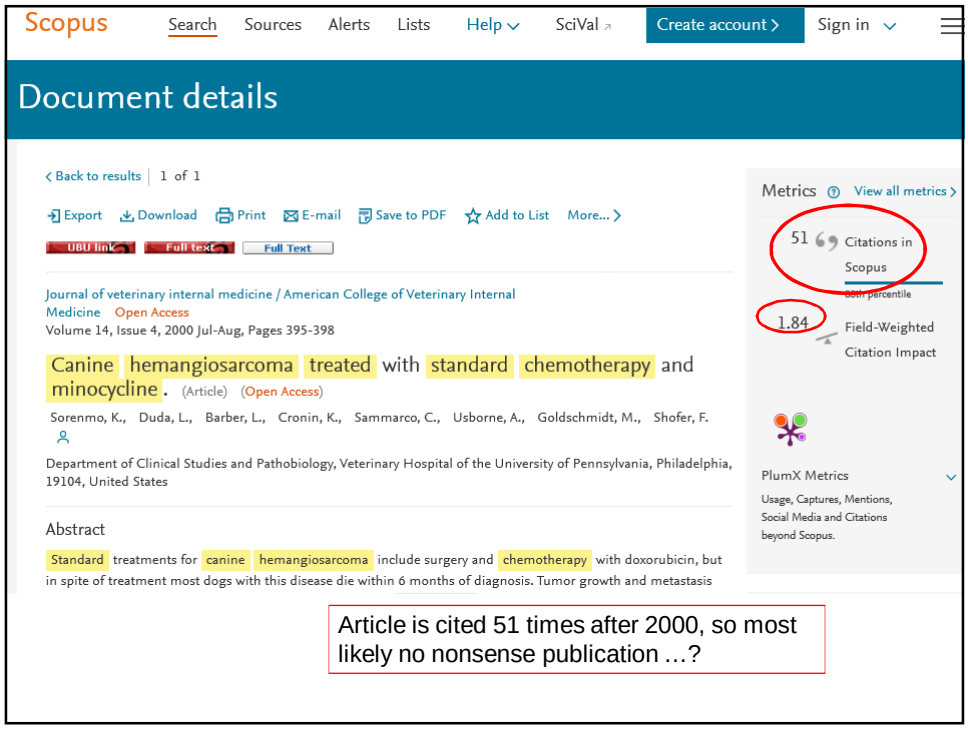
- Original research?
- Review, opinion, hypothesis?
- Peer-reviewed?
  - or invitation only
- High-impact journal?
  - author's reputation?

What kind of paper? How to evaluate quality?

- Papers and journals are judged by their citation rates, impact factors and ranking.
- Also, need to ask is this a specialist journal or general journal?
  - General journals include JAAHA, JAVMA, JSAP, VetRec, Kleintierpraxis, etc
  - Specialist journals in veterinary medicine include: VCO, JVIM, The Vet J, Vet Pathol, Vet Clin Path, etc

How to find out citation rate and impact factor?

- Scopus: => citation rate of individual article
- ISI Web of Knowledge: Journal Citation Reports => Impact Factor and Ranking of journal



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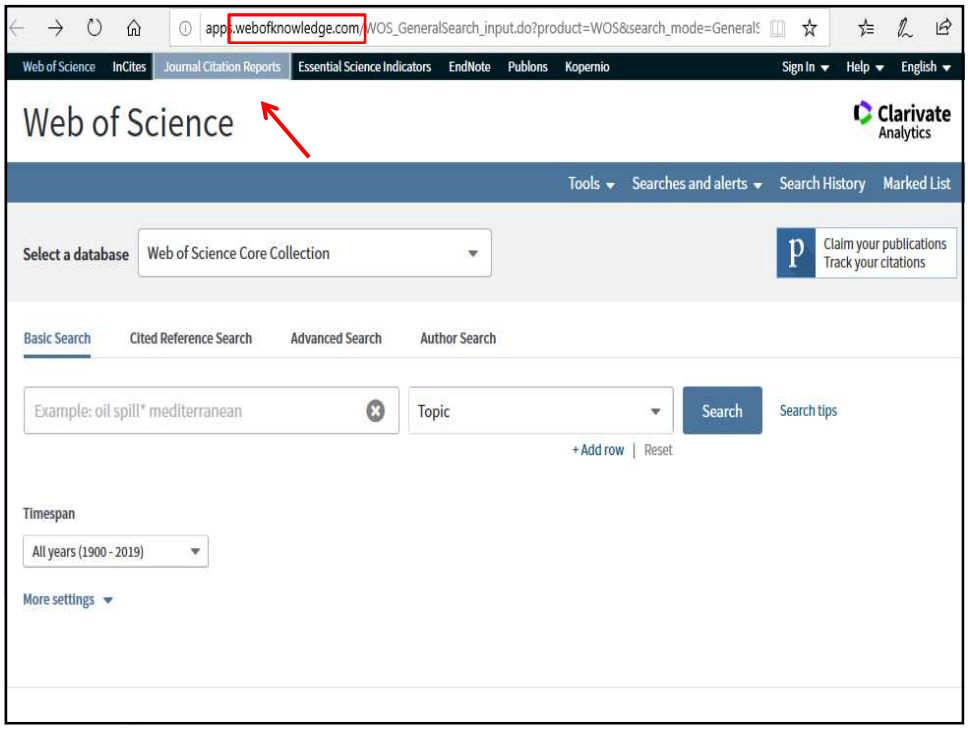

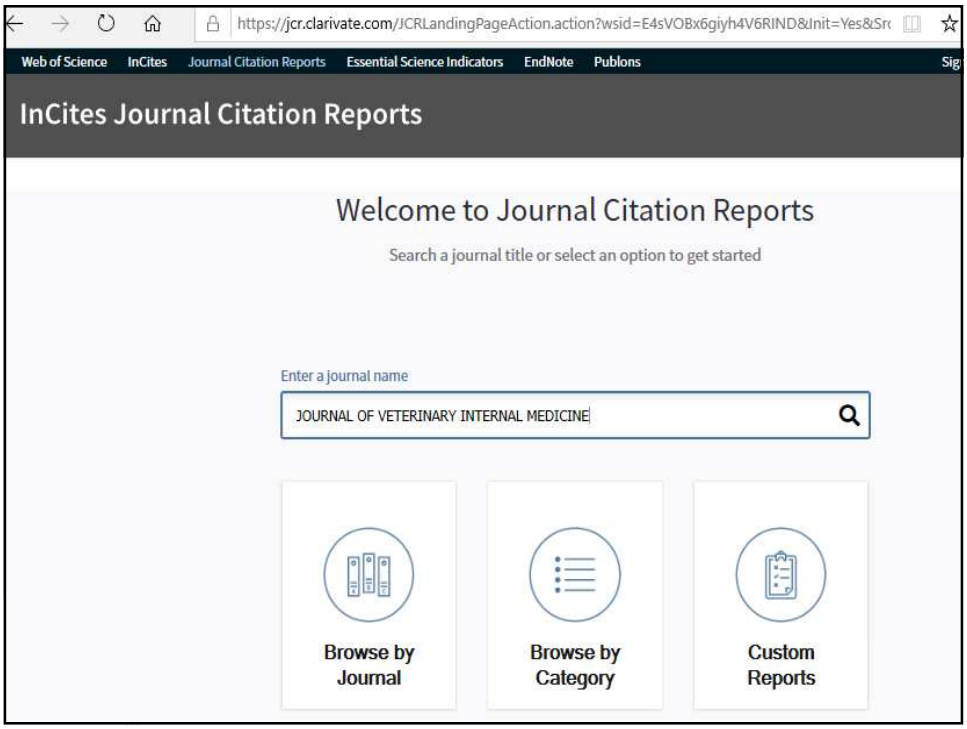
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Enter a journal name
JOURNAL OF VETERINARY INTERNAL MEDICINE
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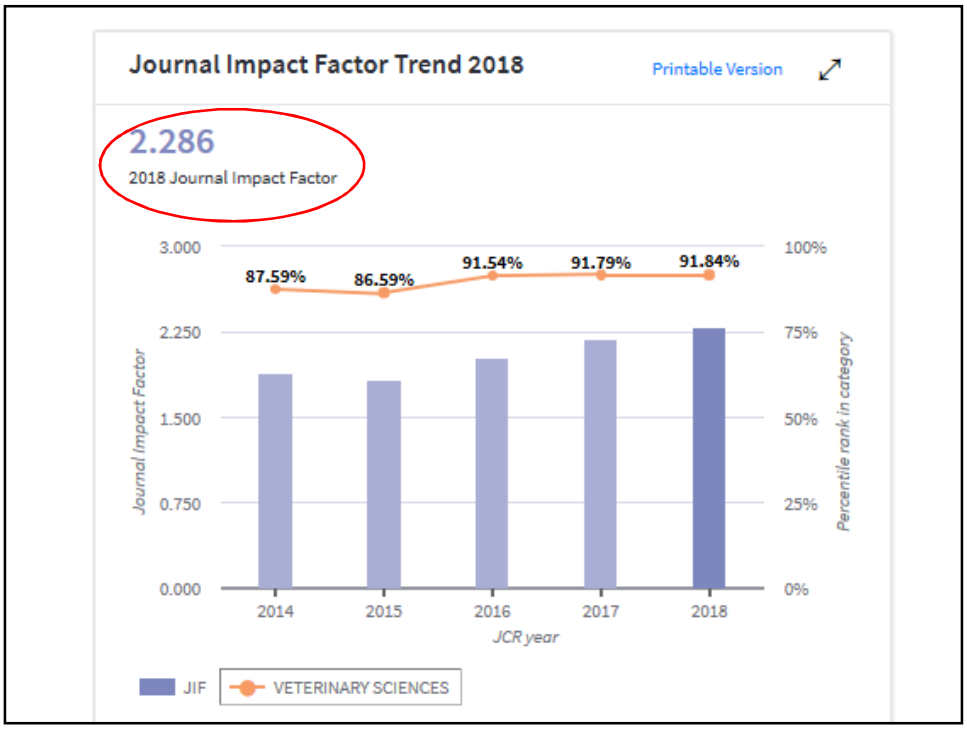
Custom Reports


Journal Impact Factor Trend 2018
Printable Version
2.286
2018 Journal Impact Factor
3.000
2.250
1.500
0.750
0.000
Journal Impact Factor
100%
75%
50%
25%
0%
Percentile rank in category
87.59%
86.59%
91.54%
91.79%
91.84%
2014
2015
2016
2017
2018
JCR year
JIF
VETERINARY SCIENCES

Calculation of Impact Factor

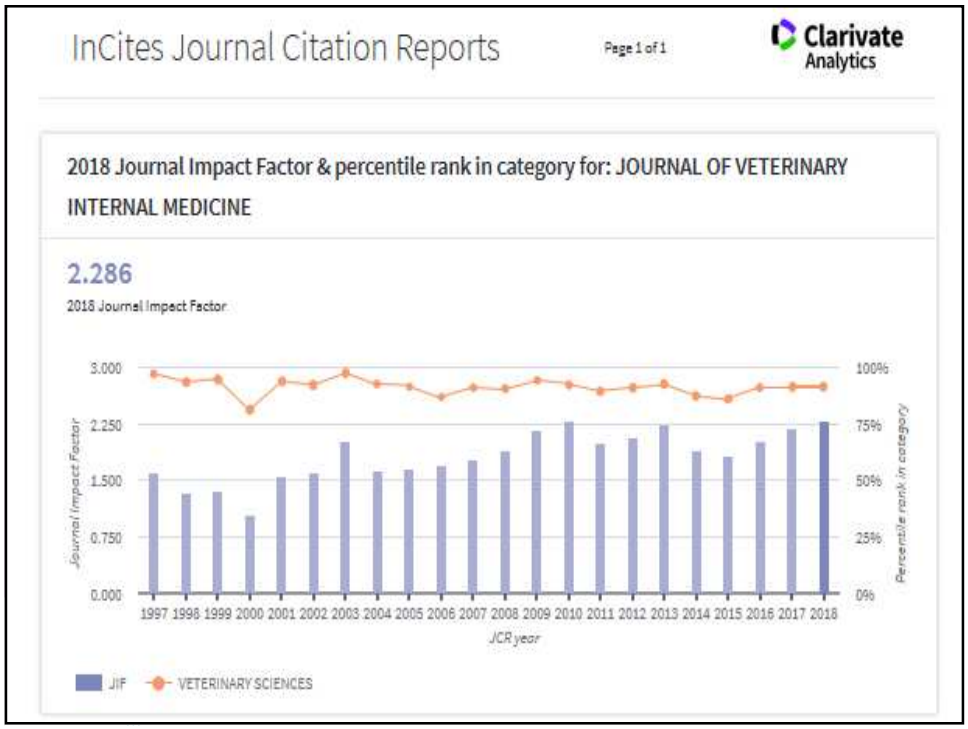
- The impact factor of a journal is calculated by dividing the number of current year citations to the source items published in that journal during the previous two years

- 2018 impact factor = A/B.

  where:

  A = the number of times that all items published in that journal in 2016 and 2017 were cited by indexed publications during 2018.

  B = the total number of "citable items" published by that journal in 2016 and 2017.


InCites Journal Citation Reports
Page 1 of 1
Clarivate Analytics
2018 Journal Impact Factor & percentile rank in category for: JOURNAL OF VETERINARY INTERNAL MEDICINE
2.286
2018 Journal Impact Factor
3.000
2.250
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0.750
0.000
Journal Impact Factor
100%
75%
50%
25%
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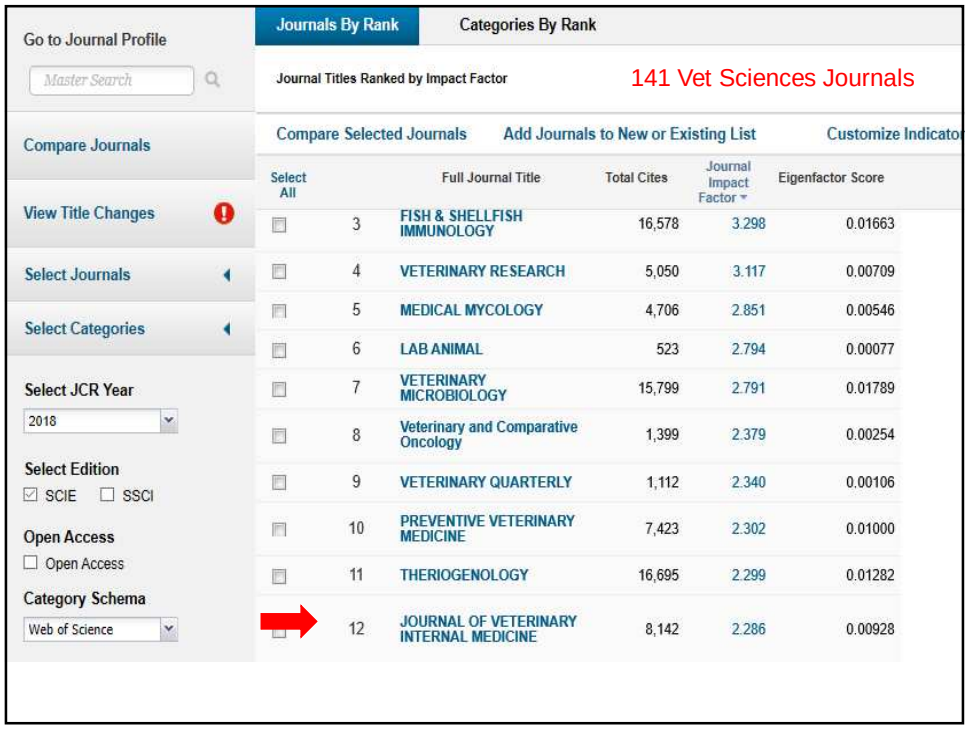
Percentile rank in category
1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018
JCR year
JIF
VETERINARY SCIENCES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Select Categories
Select JCR Year
2018
Select Edition
SCIE
SSCI
Open Access
Open Access
Category Schema
Web of Science
Journals By Rank
Categories By Rank
Journal Titles Ranked by Impact Factor
141 Vet Sciences Journals
Compare Selected Journals
Add Journals to New or Existing List
Customize Indicato
Select All
Full Journal Title
Total Cites
Journal Impact Factor
Eigenfactor Score
3 FISH & SHELLFISH IMMUNOLOGY 16,578 3.298 0.01663
4 VETERINARY RESEARCH 5,050 3.117 0.00709
5 MEDICAL MYCOLOGY 4,706 2.851 0.00546
6 LAB ANIMAL 523 2.794 0.00077
7 VETERINARY MICROBIOLOGY 15,799 2.791 0.01789
8 Veterinary and Comparative Oncology 1,399 2.379 0.00254
9 VETERINARY QUARTERLY 1,112 2.340 0.00106
10 PREVENTIVE VETERINARY MEDICINE 7,423 2.302 0.01000
11 THERIOGENOLOGY 16,695 2.299 0.01282
12 JOURNAL OF VETERINARY INTERNAL MEDICINE 8,142 2.286 0.00928

Key Indicators 2018

Impact metrics		
Total Cites	8,142	Graph
Journal Impact Factor	2.286	Graph
5 Year Impact Factor	2.491	Graph
Immediacy Index	0.410	Graph
Impact Factor Without Journal Self Cites	1.860	Graph

Source metrics		
Citable Items	239	Graph
% Articles in Citable Items	97.07	Graph
Average JIF Percentile	91.844	Graph
Cited Half-Life	9.0	Graph
Citing Half-Life	9.4	Graph

Often Impact Factor can also be found on website of Publisher

Wiley Online Library | Access by Utrecht University

Journal of Veterinary Internal Medicine — ACVIM

Edited By: Co-Editors in Chief: Stephen P. DiBartola, DVM, DACVIM, The Ohio State University and Kenneth W. Hinchcliff, BVSc, PhD, DACVIM, The University of Melbourne

Impact factor: 2.286

ISI Journal Citation Reports © Ranking: 2018: 12/141 (Veterinary Sciences)

Online ISSN: 1939-1676

Impact factor and ranking of this journal is OK.

Organization of a paper - I
IMRAD format

- Introduction: why the authors decided to conduct the research.
- Methods: how they conducted the research and analyzed their results.
- Results: what was found.
  AND
- Discussion: what the authors think the results mean.

Organization of a paper - II

- IMRAD
  - Introduction, Methods, Results and Discussion
- Plus
  - Title, abstract, authors, acknowledgements, declarations, references
  - Tables and figures; legends

Organization of a paper - III

- Variations
  - Pressures on length versus accessibility to non-expert
  - Combined Results and Discussion
  - Methods at end
  - On-line supplements
  - Other types of articles, such as case reports, reviews, and editorials, probably need to be formatted differently
  - *Science* and *Nature*

Reading a scientific paper

- This is not a novel
- No need for a linear approach
- Look at
  - Title
  - Abstract
  - Figures, tables
  - Introduction, results, discussion
  - Then methods

Reading a scientific paper

- Struggle with the paper
  - active not passive reading
  - use highlighter, underline text, scribble comments or questions on it, make notes
  - if at first you don't understand, read and re-read, spiraling in on central points

Reading a scientific paper

- Get into question-asking mode
  - doubt everything
  - nit-pick
  - find fault
  - just because it's published, doesn't mean it's right
  - get used to doing peer review

Reading a scientific paper

- Move beyond the text of the paper
  - talk to other people about it
  - read commentaries
  - consult dictionaries, textbooks, online links to references, figure legends to clarify things you don't understand

Why you are reading determines how you should read

- The abstract & introduction should tell you whether it is worth reading in depth or only worth skimming
- In addition it will also depend on what you are looking for

Critical assessment of the paper

- Read the experimental results – that is the figures and tables together with their legends – at least as closely as the main text
- Avoid reading the discussion section
- Readers should evaluate results before reading the authors' conclusions
- Use your own judgment

Evaluating a paper

- What questions does the paper address?
- What are the main conclusions of the paper?
- What evidence supports those conclusions?
- Do the data actually support the conclusions?
- What is the quality of the evidence?
- Importance of conclusions?

What questions does the paper address? (1)

- Descriptive research
  - Often in early stages of our understanding; can't formulate hypotheses until we know what is there.
    - e.g. Immunohistochemical characterization of canine indolent lymphoma
- Comparative research
  - Ask how general or specific a phenomenon is.
    - e.g. Gene expression profiling of histiocytic sarcomas in a canine model

What questions does the paper address? (2)

- Analytical or hypothesis-driven research
  - test hypotheses
    - e.g. omega-3 rich food will protect against cancer
- Methodological research
  - Find out new and better ways of doing things
  - Describe new resources
    - e.g. intraperitoneal administration of chemotherapy in cats with lymphoma
- Many papers combine all of the above

The places to find information about a paper's subject matter

- The title
- The abstract
- The introduction

Note
The discussion contains further ideas, but it is not worth reading the discussion in any detail until we have a good idea what is being discussed.

Title

- Try to be specific
  - Not: A study into the safety of chlorambucil in CLL
  - But: Chlorambucil has little side effects in the treatment of CLL in dogs
- Always mention species in which study was performed => publication will be cited more often!

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rsos.royalsocietypublishing.org

Brief report

Cite this article: Letchford A, Moat HS, Preis T. 2015 The advantage of short paper titles. *R. Soc. open sci.* **2**: 150266. http://dx.doi.org/10.1098/rsos.150266

Received: 26 June 2015
Accepted: 27 July 2015

The advantage of short paper titles

Adrian Letchford, Helen Susannah Moat and Tobias Preis

Data Science Lab, Behavioural Science, Warwick Business School, University of Warwick, Coventry CV4 7AL, UK

Vast numbers of scientific articles are published each year, some of which attract considerable attention, and some of which go almost unnoticed. Here, we investigate whether any of this variance can be explained by a simple metric of one aspect of the paper's presentation: the length of its title. Our analysis provides evidence that journals which publish papers with shorter titles receive more citations per paper. These results are consistent with the intriguing hypothesis that papers with shorter titles may be easier to understand, and hence attract more citations.

The advantage of short paper titles

"Our analysis suggests that papers with shorter titles do receive greater numbers of citations. However, it is well known that papers published in certain journals attract more citations than papers published in others. When citation counts are adjusted for the journal in which the paper is published, we find that the strength of the evidence for the relationship between title length and citations received is reduced.

Our results do however reveal that journals which publish papers with shorter titles tend to receive more citations per paper."

Authors

- Who are the authors? Do they have a track record on the topic?
- Which institutes?

Abstract & Introduction

- The abstract and introduction help you to decide whether, why and how to read
- Abstract should give you a brief summary of why the study was performed and the paper's main finding (often word limitation 250-300)
- Some journals do not accept P-values in abstract anymore
- Introduction provide a background to the paper and a rationale for the investigation in more detail
- Don't write a text book chapter on the topic in the Introduction

Introduction

- Background information with relevant references
- Rationale of the study
  - What gap of knowledge?
  - What controversy?
- Aim(s) of the study
- Brief, clear, to the point

Introduction: common problems

- Too long
- Historical details
- Too general and vague
- Imitative
- Contains “Discussion” material

Why it is good idea to read introductions

- They give you some idea what background information you need before starting
- They give you an insight into the authors' starting point and approach to the subject

In Summary

- The Abstract and Introduction should explain why the paper was written
- They do not give detailed information, but should help you decide how much time to spend on the paper
- Introductory sections are an entry into a paper – never substitute for reading the paper properly

Why it is good idea to read Materials and Methods

- To know how it was done in order to understand what it means
- If you want to replicate an experiment, the methods section is indispensable
- To find stimulating ideas and make connections between different areas
- To adapt methodological approaches to our own experiments
- To find potential flaws in the study

Methods

- Who? What? When? Where? How?, Why?
- Study design
- Study material (what did you work with?)
- What was done to the study material (intervention)?
- How was the effect assessed (outcome measures)?
- Analysis and statistical methods
- Ethical considerations

Methods: Study design

- Case-control, cohort, cross-sectional
- Prospective, retrospective
- Controlled, uncontrolled
- Randomized, non-randomized
- Open, Blinded (single or double)

Results

- Results of all experiments in natural order
- In subsections similar to methods
- Cite all tables/figures in text
- Text, tables and figures do not duplicate
- Statistical analysis

Results

Data collection and recruitment (Response rate)

Study group
Number, baseline characteristics Drop-outs, withdrawals
Absent data on some subjects

Key findings
Primary outcome measures

Secondary findings
Secondary outcome measures Subgroup analyses

Results

- Should not include any methods or data which were not included in the M&M section
- Interpretation of data (--> discussion)
- References
- Careful with use of words like significant, random, correlation

Discussion

- Recapitulation of major findings
- Discussion of findings cf. available data
- Why the difference, why more reliable, etc
- Discussion of important minor findings
- Alternative explanations
- Strength and pitfalls
- Implications of the findings
- Unanswered questions and future research
- Final summary / conclusion

Discussion

Should NOT include

- History
- Repetition of results
- Discussion of points other than those generated by the study's data
- Unreasonable extrapolation of results, Superlatives

Evaluating the Medical Literature critically

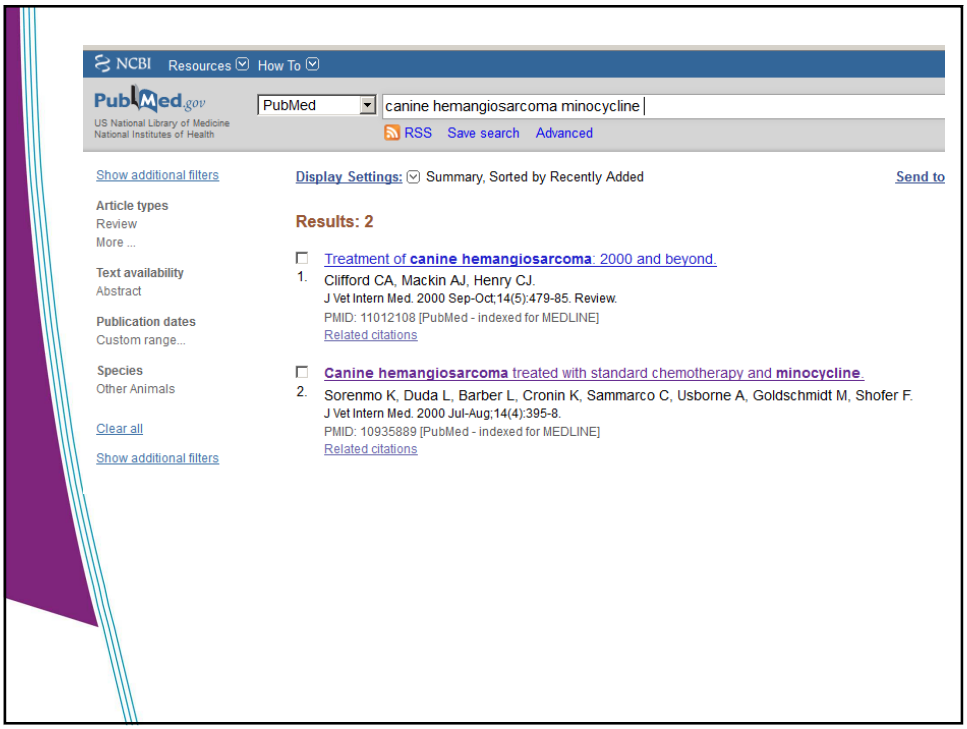
-

PP-ICONS: another tool to help to quickly scan an article to see if it will help us with our PICO question

PP-ICONS

- Problem
- Patient or population
- Intervention
- Comparison
- Outcome
- Number of subjects
- Statistics

Flaherty, Robert J. A simple method for evaluating the clinical literature. Fam Prac Mgt, May 2004;47-52. Available online at http://www.aafp.org/fpm/20040500/47asim.html.



Problem (PP-ICONS)

- What is the clinical condition that was studied in the article?

  OBJECTIVE: To evaluate the efficacy of chemotherapy with doxorubicin and minocycline, an antiangiogenic agent, in dogs with hemangiosarcoma

- The problem studied should be sufficiently similar to your clinical problem, or the results will not be relevant.

Patient or Population (PP-ICONS)

- Is the study group similar to your patient or practice?

  PATIENTS: A total of 18 patients with different forms of hemangiosarcomas (including splenic and subcutaneous)

- *If the patients in the study are not similar to your patient (older, sicker, different gender or more clinically complicated), the results may not be relevant.*

Intervention (PP-ICONS)

- Is the intervention the same as what you are looking for?

  TREATMENT: In splenic HSA surgery + CT + Minocycline, in other dogs no surgery.

  - *If not the same, at least comparable?*

Comparison (PP-ICONS)

- The comparison is what the treatment is tested against.
  - Could be another therapy, placebo, or no treatment at all.

COMPARISON: Historical control group (n=16) with different types of HSA treated with surgery + chemotherapy

Outcome (PP-ICONS)

- Response rates
- Response durations
- Survival
- Toxicities
- Cost reductions
- etc

MAIN OUTCOME MEASURE: Overall survival

Number (PP-ICONS)

- Number of subjects in the study is crucial in whether accurate statistics can be generated from the data.
  - Too few patients may not be enough to show that a difference really exists between intervention and comparison groups (power of a study).
  - Many human studies therefore contain more than 400 subjects, which is usually adequate to provide reliable statistics.

18 patients completed the study

Number (PP-ICONS)

- Are statistical measures straightforward and applicable (i.e., absolute risk reduction/numbers needed to screen/adequate survival analysis, etc)?

STATISTICS: The Kaplan-Meier product limit method was used to estimate the portion of dogs that were alive or had died. Log rank test was used to test differences in survival. Significant is $P<0.05$.

Clinical trials

Basis of many EBVM data

Clinical trial/ Therapeutic experiment

Every form of planned experiment with patients which is designed to discover the most suitable treatment for future patients

Clinical trials

- Phase 1 trials: dose-finding, toxicology/pharmacology
- Phase 2 trials: small-scale, effectivity
- Phase 3 trials: large-scale, effectivity, control group
  - Additional objectives: toxicity, prognostic factors
- Phase 4 trials: post marketing, long term effects

Estimation efficacy

- 12 of 20 dogs responded well on treatment
- Is this good?
- Compare with something else

Phase 3: control group

- Untreated
- Historical
- Placebo
- Other therapy (e.g. most common)

Which patients in trial?

- All animals presented with this disease?
- Only the poor performance patients?
- Only the good performance patients?
- Uniform population (age, sex, breed)?
- Are they allowed to have another disease?

Inclusion and exclusion criteria

- Histologic/cytologic proven diagnosis
- Stage 3,4 or 5
- Multicentric lymphoma in dogs
- Pregnant dogs
- Dogs with previous malignancies
- Dogs pretreated with prednisone
- Dogs with a concurrent life-threatening disease (e.g. congestive heart failure)

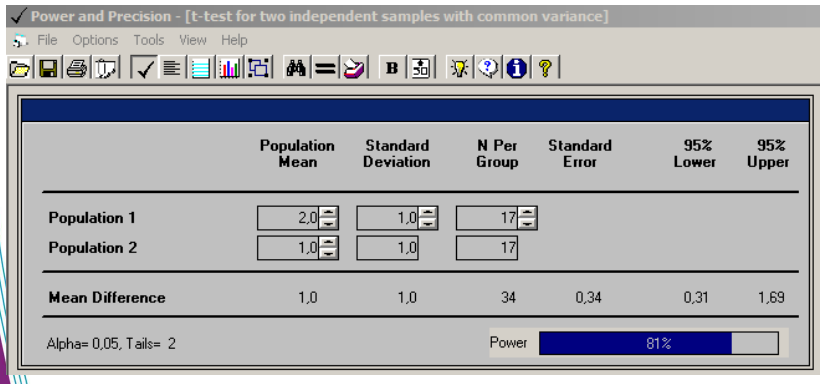
In which treatment group?

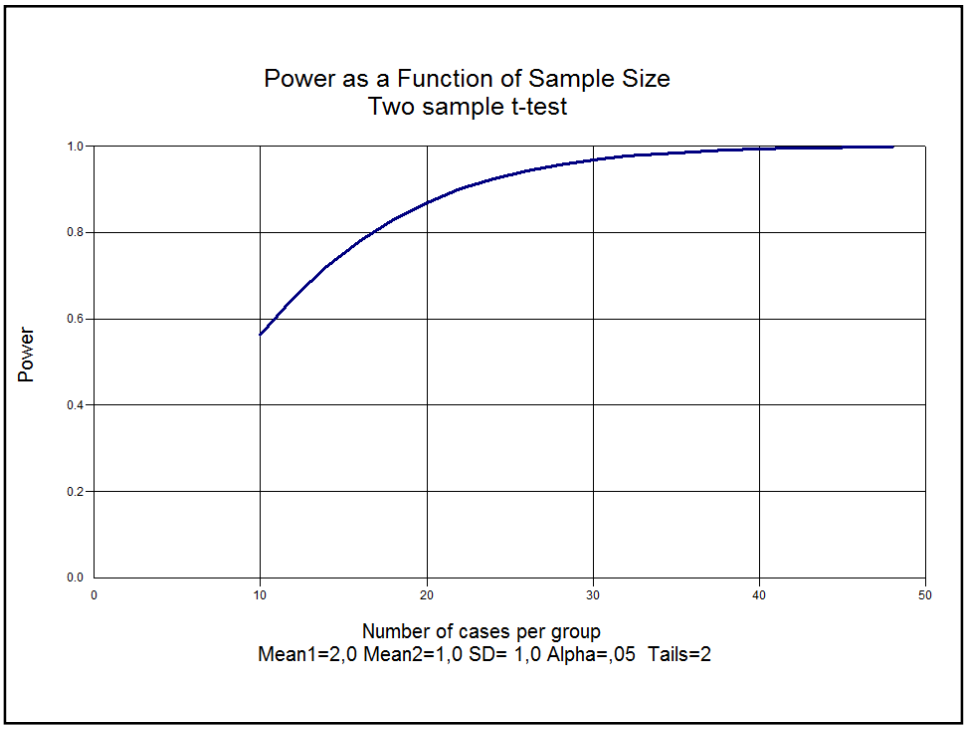
- Ask owner
- Alternately
- Randomization
  - With tables: e.g. AABABBBABABAA
  - With extra groups: BDDACCADBBAA
    - Two groups for each treatment arm

How many patients in trial?

- Power analysis (a priori: beforehand)
- Depends on:
  - To be expected difference between groups and variability of characteristic
  - Acceptable error of positive finding (**α or Type I error**; usually P<0.05) (*i.e. concluding that a treatment has an effect when it does not*)
  - Failing to detect a difference when in reality there is (**β or Type II error**; usually set at 0.20 or 0.10
  - **Power**: Probability of being able to detect the specified effect (1-β; usually set at 80% or 90%)

Poweranalysis with statistical software





Evaluation of results

- Toxicities
- Performance improvement (score)
- Disappearance of tumor (partial or complete remission)
- Normalization of blood values
- Ultrasound parameters
- Disease Free Period / Progression Free Period
- Survival

How to evaluate qualitative data outcome?

- Toxicity
- Clinical symptoms
- ….

Try to make a more objective scale

Examples toxicity grading

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Anorexia/ vomiting	None	Anorexia	Transient vomiting	Therapy needed	Constant vomiting
Diarrhea	None	< 2 days	> 2 days	Therapy needed	Hemaorrhagic Dehydration
Alopecia	None	Minimal	Focal	Complete Reversible	Complete Irreversible
Hematocrit	>0.36	0.29-0.36	0.24-0.28	0.19-0.23	<0.19
Leukocyes	>4.0	3.0-3.9	2.0-2.9	1.0-1.9	<1.0
Thrombocytes	>100	75-99	50-74	25-49	<25

Example Scoring Index

- Scaly skin:
  - Severe: 3 points; moderate: 2 points; some: 1 point; none: 0 points
- Scratching:
  - Severe: 6 points; moderate: 3 points; none: 0 points
- Licking feet
  - Frequent: 2 points; some: 1 point; none: 0 points
- Rubbing face on floor
  - Frequent: 2 points; some: 1 point; none: 0 points

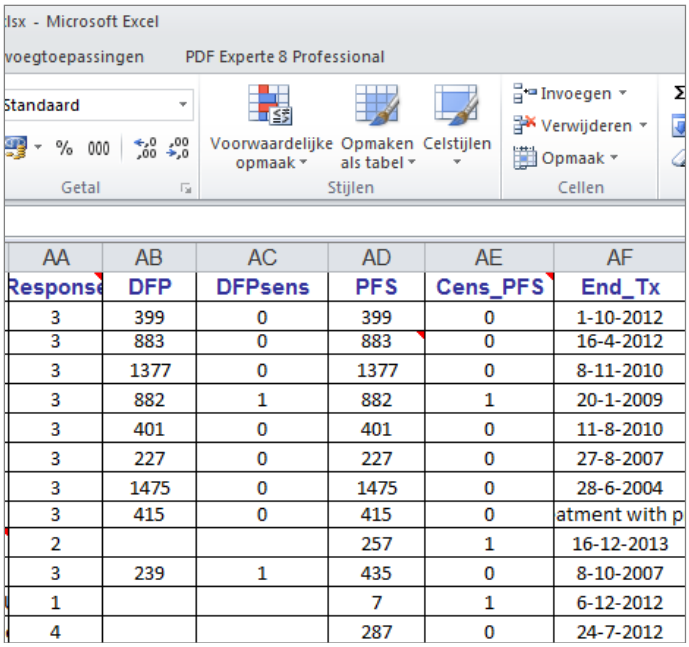
Disease Free Period/Survival

- Group A: 2, 2, 4, 6, 8, 10, 14, 67 weeks
- Group B: 3, 5, 7, 9, 11, 15, 17, 18 weeks
- Mean:
  - Group A: 14,1 weeks
  - Group B: 10,6 weeks
- Median:
  - Group A: 9 weeks
  - Group B: 10 weeks

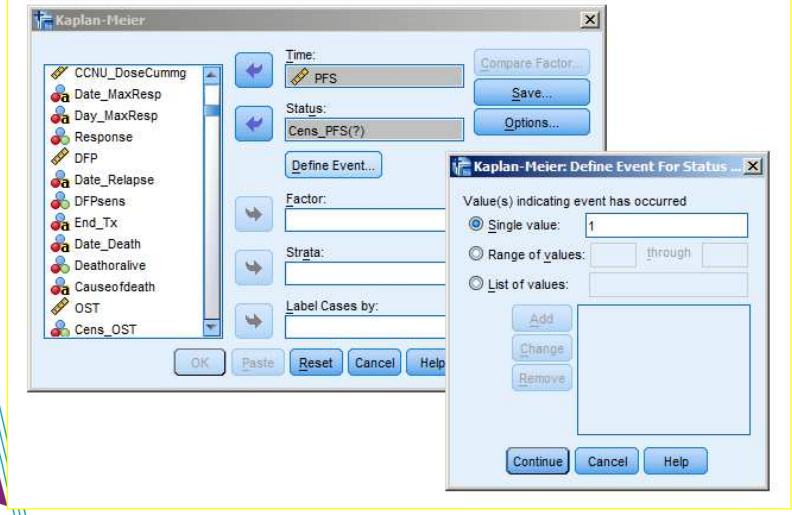
- Survival curves; censoring; Log-rank test

Censoring

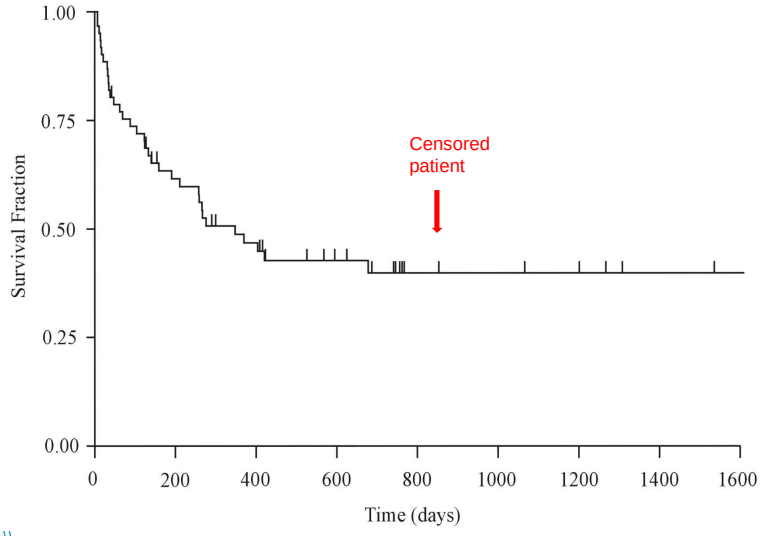
- There are usually some individuals who do not experience the event during the study, so the time to event is incomplete for these cases. The researcher knows it is greater than the length of time these individuals were studied, though not how much greater.
- Can be both for overall survival as well as DFP, PFS, etc.
- If this occurs: censor = 0 otherwise censor = 1

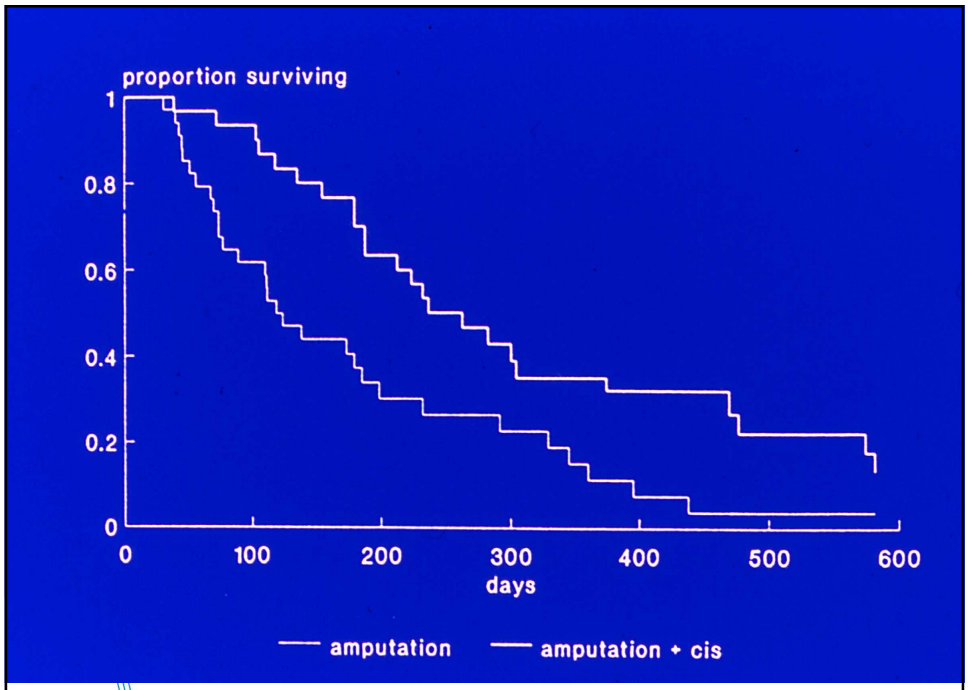


AA	AB	AC	AD	AE	AF
Response	DFP	DFPsens	PFS	Cens_PFS	End_Tx
3	399	0	399	0	1-10-2012
3	883	0	883	0	16-4-2012
3	1377	0	1377	0	8-11-2010
3	882	1	882	1	20-1-2009
3	401	0	401	0	11-8-2010
3	227	0	227	0	27-8-2007
3	1475	0	1475	0	28-6-2004
3	415	0	415	0	atment with p
2			257	1	16-12-2013
3	239	1	435	0	8-10-2007
1			7	1	6-12-2012
4			287	0	24-7-2012



Kaplan Meier Survival curve





Differences between survival curves can be analysed by log-rank test

Prognostic factors

- Factors that can be important before start of treatment to predict outcome of treatment
  - Response is therefore no real prognostic factor
- Can be important to make treatment choice
- Can be identified by univariate and/or multivariate analysis
- Multivariate analysis corrects for confounders

Confounders

- There is confounding when a third factor, which is related to both the determinant as to the outcome, upsets the causal link between the two.
- Example:

  Hypercalcemia is negative prognosticator in lymphoma in dogs; Hypercalcemia is related to T-cell lymphoma; T-cell lymphomas have worse prognosis.

Short Intermezzo

Writing abstracts for congress

What can go wrong? (1)

- Read the instructions for format: Title, authors, Institutions, format of abstract!!!!
- Stick to maximal number of words. Count them!
- Correct (or let someone correct) English
- Use scientific language: “we have looked at the data and…” => “Data were analysed by…”

What can go wrong? (2)

- Lack of objective or hypothesis for the study
- Lack of coherence between objective/hypothesis and conclusions of the study
- Study described is similar to publications already available in the literature, no justification for present study
- No proper study design
- No P-values to support statistical significance

Articles

Determination of carcinoembryonic antigen and cancer antigen (CA 15-3) in bitches with tumours on mammary gland: preliminary report

Abstract

The aim of this work was to determine levels of carcinoembryonic antigen (CEA) and cancer antigen (CA 15-3) in the blood serum of 45 bitches. A modified procedure was used to determine the CEA and CA 15-3 markers with the human kits using the radioimmunoassay method. Samples collected from extirpated tumour of mammary glands were histologically processed and classified as per WHO guidelines. The average age of animals with tumour was 10.00 ± 2.2 years; for healthy bitches average age was 4.2 ± 3.2 years. Values of CEA and CA 15-3 were considered positive, if they exceeded 0.23 ng mL^{-1} and 7 IU mL^{-1}, respectively. Average levels of CEA in the tumour group were 0.25 ± 0.06 versus 0.20 ± 0.03 in healthy bitches ($P = 0.0001$). The average CA 15-3 value in bitches with tumour was 8.58 ± 1.27 versus 5.14 ± 1.34 in healthy animals ($P < 0.0001$).

- No reason in Title and Abstract why this was done
- No conclusion what to do with it
- No species listed in title and abstract

Determination of carcinoembryonic antigen and cancer antigen (CA 15-3) in bitches with tumours on mammary gland: preliminary report

Introduction:
CEA and CA 15-3 are serum markers for human breast cancer patients

Aim of present study:
1) Verify if human IRMA kits for CEA and CA 15.3 can be used in the dog
2) Determine levels of CEA and CA 15.3 in clinically healthy bitches
3) Determine levels of CEA and CA 15.3 markers in bitches with mammary gland tumours

M&M

- 20 healthy bitches and 25 dogs with mammary tumours (24 dogs with a malignant tumour, including carcinomas and sarcomas; and 2 dogs with a benign tumour: hemangioma, myxochrondroma)
- Mean age (sd): Healthy dogs 4.3 years (s.d. 3.2), tumour dogs 10.0 years (s.d. 2.2). $P<0.001$.

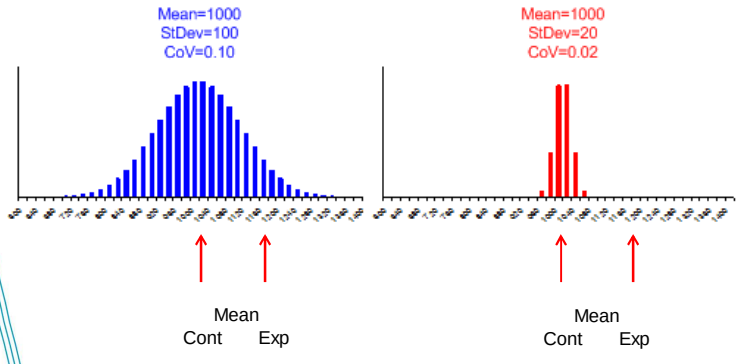
IRMA kits

- Detection limits for [CEA] in the dog 0.10 ng/ml and for [CA 15-3] 2.0 IU/ml
  - Question: Is this sensitive enough?
- Calibration curves 0.1-105 ng/ml and 2-100 IU/ml, respectively
  - Question: Is this range adequate?
- CVs 6.8% and 4.7%, respectively
  - Question: Is this CV small enough to detect differences?

Coefficient of Variation

(Measurement of imprecision)

- CV = standard deviation / mean



Coefficient of Variation

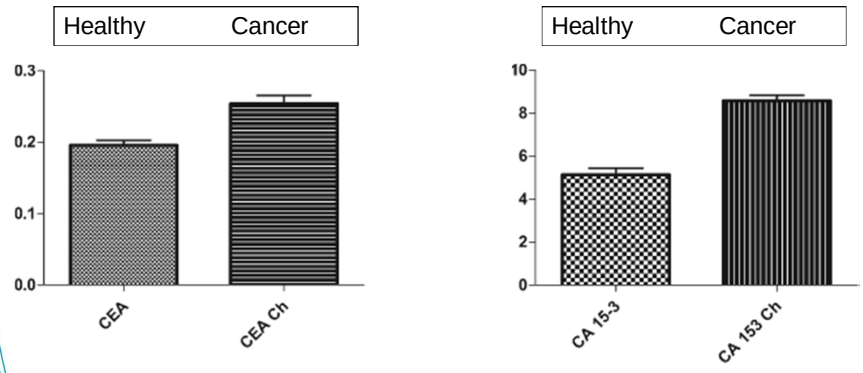
- <5% for automated assays and <10% for manual assays
- < 1/8 of width of reference range expressed as a percentage of the mean of the range
- Imprecision should be less than 0.5x biological CV (between and in between patients CV)

Table 3. Statistical evaluation of the measured CEA and CA 15-3 values in clinically healthy bitches and bitches with mammary gland tumour

	CEA		CA 15-3	
	Healthy bitches	Diseased bitches	Healthy bitches	Diseased bitches
Minimum	0.1300	0.1800	3.020	7.100
Maximum	0.2300	0.4200	7.700	11.20
Mean	0.1955	0.2538 *	5.138	8.577 *
SD	0.03137	0.05671	1.339	1.270
95% Percentile	0.2295	0.4025	6.790	11.19
Cut off values	0.20-0.23		5.0-7.0	

- *: P<0.001
- Sensitivity for *CEA* to detect mammary carcinoma 60% and for *CA 15-3* 100%; specificity both 95%
- ET: not tested in benign tumours!!!!!!!!
- ET: Cut-off values a range, not a calculated single value! (Due to column statistics?)

Determination of carcinoembryonic antigen and cancer antigen (CA 15-3) in bitches with tumours on mammary gland: preliminary report



Expressed in Bar Graphs

Veterinary and Comparative Oncology
Volume 12, Issue 3, pages 205-214, 4 SEP 2012 DOI: 10.1111/j.1476-5829.2012.00353.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1476-5829.2012.00353.x/full#vco353-fig-0001

Reference values

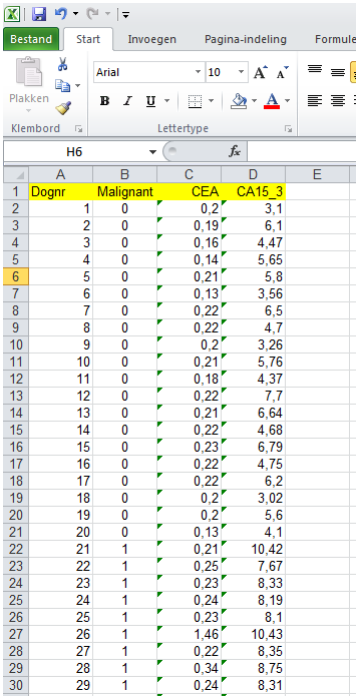
- CEA:
  - 0.0-0.20 ng/ml
  - Detection limit 0.1 ng/ml
  - Only 10/20 of healthy dogs within reference values
  - MedCalc:
- CA 15-3:
  - 0.0-5.0 IU/ml
  - Detection limit 2 IU/ml
  - Only 10/20 of healthy dogs within reference values
  - MedCalc:

Table 1. Anamnestic data and average values of CEA and CA 15-3 markers in clinically healthy bitches

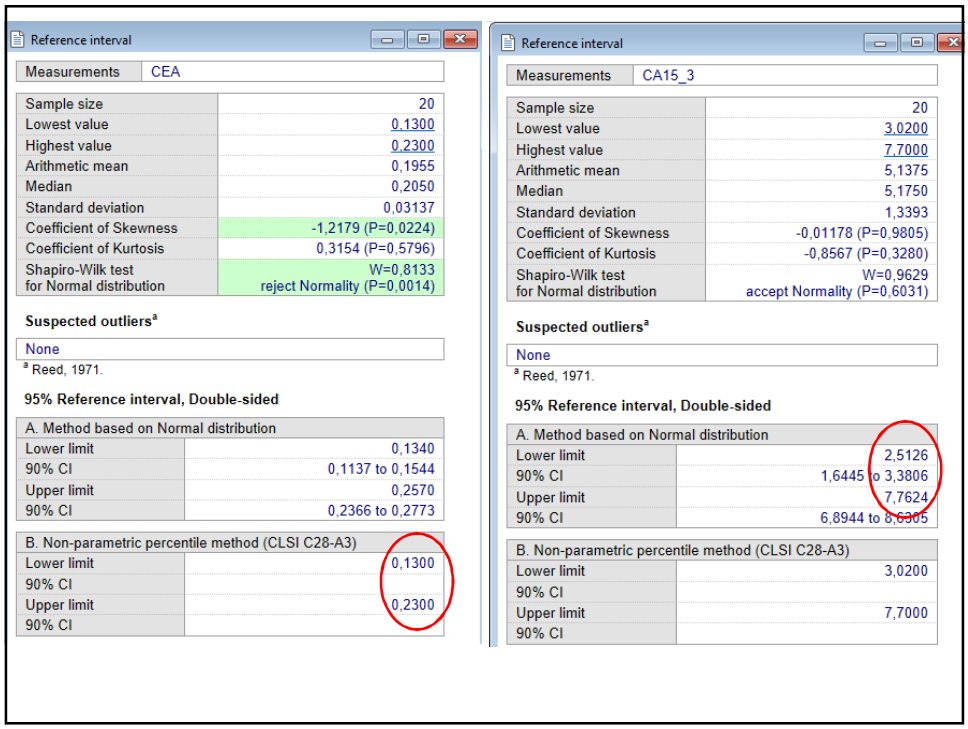
No.	Personal data	Spayed Yes/No	CEA ng mL^{-1}	CA 15-3 IU mL^{-1}
1.	JRT, 3 years	N	0.20	3.10
2.	X, 1.5 years	N	0.19	6.10
3.	Beagle, 10 months	N	0.16	4.47
4.	Poodle , 7 years	N	0.14	5.65
5.	X, 3 years	Y	0.21	5.80
6.	American Staffordshire terrier, 4 years,	N	0.13	3.56
7.	GS, 10 months	N	0.22	6.50
8.	GS, 1 year,	N	0.22	4.70
9.	Doberman Pinscher, 6 years	N	0.20	3.26
10.	GS, 1.5 years	N	0.21	5.76
11.	American Staffordshire terrier, 10 years	N	0.18	4.37
12.	Doberman Pinscher, 5 years	N	0.22	7.70
13.	Doberman Pinscher, 8 years	N	0.21	6.64
14.	GS, 4–5 years	N	0.22	4.68
15.	RTW, 3 years	N	0.23	6.79
16.	x RTW, 3–4 years	N	0.22	4.75
17.	Labrador Retriever, 11 years	Y	0.22	6.20
18.	Tibetan Mastiff, 2 years	N	0.20	3.02
19.	RTW, 2 years	N	0.20	5.60
20.	Golden Retriever, 8 years	Y	0.13	4.10

Table 2. Anamnestic data, TNM system, average values of CEA/CA 15-3, histo gland tumour

No.	Personal data	Spayed Yes/No	TNM System	CEA ng mL^{-1}	CA 15-3 IU mL^{-1}
1.	X, 7 years	N	T1N0M0	0.21	10.42
2.	GS, 6 years	N	T1N0M0	0.25	7.67
3.	X, 7 years	N	T3N0M0	0.23	8.33
4.	GS, 10 years	N	T2N0M0	0.24	8.19
5.	X, 7 years	N	T3N0M0	0.23	8.10
6.	X, 12 years	N	T2N0M0	1.46	10.43
7.	Longhaired dachshund, 13 years	N	T1N0M0	0.22	8.35
8.	X, 9 years	N	T2N0M0	0.34	8.75
9.	Slovakian hound, 10.5 years	N	T3N0M0	0.24	8.31
10.	X, 11 years	N	T3N0M0	0.24	11.18
11.	GS, 10 years	N	T2N0M0	0.21	8.16
12.	Cocker Spaniel, 11 years	N	T2N0M0	0.22	8.36
13.	Cocker Spaniel, 10 years	N	T2N0M0	0.24	8.85
14.	Cocker Spaniel, 9 years	N	T2N0M0	0.26	7.25
15.	GS, 13 years	N	T3N0M0	0.25	10.90
16.	Cocker Spaniel, 7 years	N	T2N0M0	0.26	8.00
17.	Poodle, 12 years	N	T3N0M0	0.22	7.35
18.	Golden Retriever, 13 years	N	T3N0M0	0.21	11.20
19.	GS, 9 years	N	T2N0M0	0.28	7.20
20.	Cocker Spaniel, 10 years	N	T1N0M0	0.24	8.45
21.	X, 9–10 years	N	T2N0M0	0.35	7.10
22.	Poodle, 14 years	N	T2N0M0	0.20	7.62
23.	X, 11 years	N	T1N0M0	0.18	8.16
24.	Poodle, 10 years	N	T1N0M0	0.42	8.99
25.	X, 9 years	N	T3N0M0	0.35	7.10



	A	B	C	D	E
1	Dognr	Malignant	CEA	CA15_3	
2	1	0	0,2	3,1	
3	2	0	0,19	6,1	
4	3	0	0,16	4,47	
5	4	0	0,14	5,65	
6	5	0	0,21	5,8	
7	6	0	0,13	3,56	
8	7	0	0,22	6,5	
9	8	0	0,22	4,7	
10	9	0	0,2	3,26	
11	10	0	0,21	5,76	
12	11	0	0,18	4,37	
13	12	0	0,22	7,7	
14	13	0	0,21	6,64	
15	14	0	0,22	4,68	
16	15	0	0,23	6,79	
17	16	0	0,22	4,75	
18	17	0	0,22	6,2	
19	18	0	0,2	3,02	
20	19	0	0,2	5,6	
21	20	0	0,13	4,1	
22	21	1	0,21	10,42	
23	22	1	0,25	7,67	
24	23	1	0,23	8,33	
25	24	1	0,24	8,19	
26	25	1	0,23	8,1	
27	26	1	1,46	10,43	
28	27	1	0,22	8,35	
29	28	1	0,34	8,75	
30	29	1	0,24	8,31	



Reference interval

Measurements	CEA

Sample size	20
Lowest value	0,1300
Highest value	0,2300
Arithmetic mean	0,1955
Median	0,2050
Standard deviation	0,03137
Coefficient of Skewness	-1,2179 (P=0,0224)
Coefficient of Kurtosis	0,3154 (P=0,5796)
Shapiro-Wilk test for Normal distribution	W=0,8133 reject Normality (P=0,0014)

Suspected outliers[a]

None

[a] Reed, 1971.

95% Reference interval, Double-sided

A. Method based on Normal distribution	
Lower limit	0,1340
90% CI	0,1137 to 0,1544
Upper limit	0,2570
90% CI	0,2366 to 0,2773

B. Non-parametric percentile method (CLSI C28-A3)	
Lower limit	0,1300
90% CI	
Upper limit	0,2300
90% CI	

Reference interval

Measurements	CA15_3

Sample size	20
Lowest value	3,0200
Highest value	7,7000
Arithmetic mean	5,1375
Median	5,1750
Standard deviation	1,3393
Coefficient of Skewness	-0,01178 (P=0,9805)
Coefficient of Kurtosis	-0,8567 (P=0,3280)
Shapiro-Wilk test for Normal distribution	W=0,9629 accept Normality (P=0,6031)

Suspected outliers[a]

None

[a] Reed, 1971.

95% Reference interval, Double-sided

A. Method based on Normal distribution	
Lower limit	2,5126
90% CI	1,6445 to 3,3806
Upper limit	7,7624
90% CI	6,8944 to 8,6305

B. Non-parametric percentile method (CLSI C28-A3)	
Lower limit	3,0200
90% CI	
Upper limit	7,7000
90% CI	

Reference values

- CEA:
  - 0.0-0.20 ng/ml
  - Detection limit 0.1 ng/ml
  - Only 10/20 of healthy dogs within reference values
  - MedCalc: ref values: 0.13-0.23 ng/ml (non-parametric)
- CA 15-3:
  - 0.0-5.0 IU/ml
  - Detection limit 2 IU/ml
  - Only 10/20 of healthy dogs within reference values
  - MedCalc: ref values: 2.5-7.8 IU/ml (parametric)

What is sensitivity and specificity?

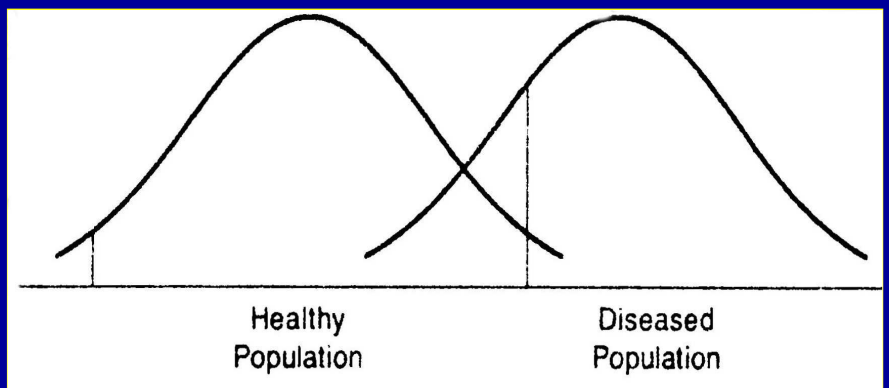
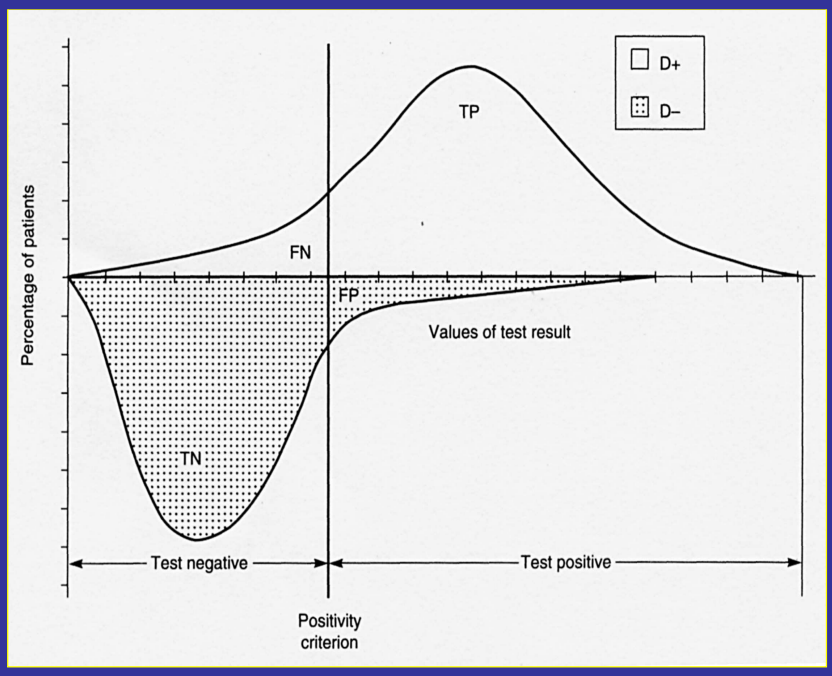


Fig. 5. Overlapping Gaussian distributions of one analyte for a diseased population and a healthy, non-diseased population with reference range shown.



Sensitivity:

Percentage of diseased animals with a positive test result

Specificity:

Percentage of healthy animals with a negative test result

	DISEASE		
TEST	Present	Absent	Total
Positive	a	b	a+b
Negative	c	d	c+d
Total	a+c	b+d	a+b+c+d

Sensitivity: a/(a+c)

Specificty: d/(b+d)

Total Accuracy: (a+d)/(a+b+c+d)

Positive predictive value:

Probability of the presence of disease when test result is positive

Negative predictive value:

Probability of the absence of disease when test result is negative

	DISEASE		
TEST	Present	Absent	Total
Positive	a	b	a+b
Negative	c	d	c+d
Total	a+c	b+d	a+b+c+d

Sensitivity: a/(a+c)

Specificty: d/(b+d)

Positive predictive value: a/(a+b)

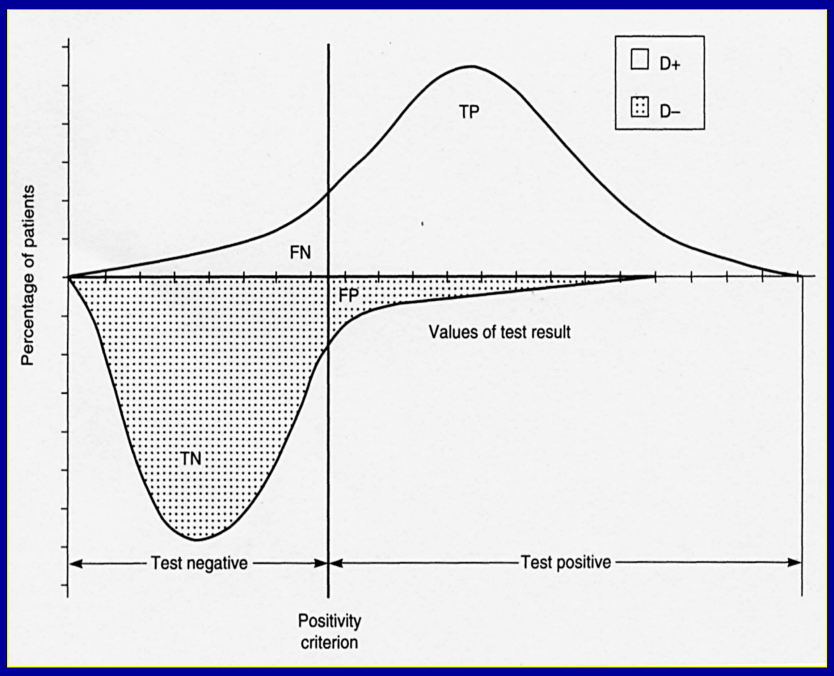
Negative predictive value: d/(c+d)

Total Accuracy: (a+d)/(a+b+c+d)

- Sensitivity and specificity are test characteristics: they remain the same when test in repeated under same conditions
- Predictive values are dependent on prevalence of disease in population tested

	DISEASE		
TEST	Positive	Negative	Pred Value
Positive	225	225	225/450= 50%
Negative	25	525	525/550= 95%
	Se = 225/250 = 90%	Sp = 525/750 = 70%	

	DISEASE		
TEST	Positive	Negative	Pred Value
Positive	225	29925	225/30150= 0.75%
Negative	25	69825	69825/69850= 99.96%
	Se = 225/250 = 90%	Sp = 69825/99750 = 70%	



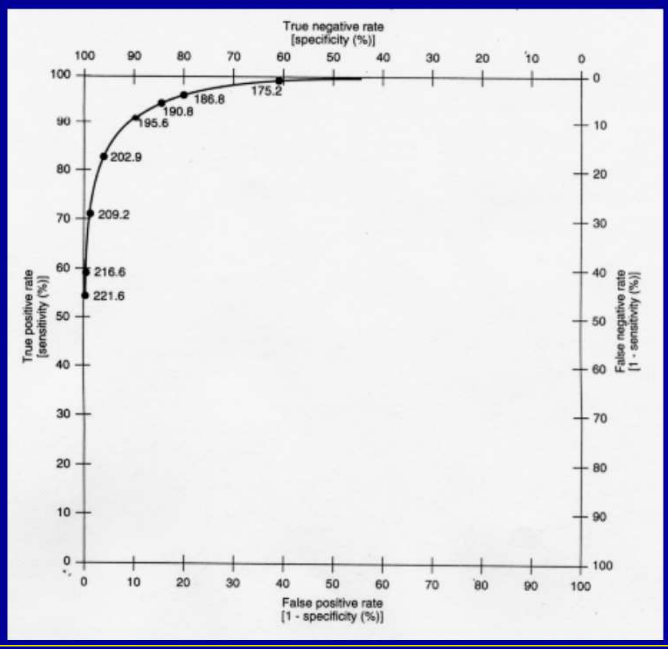
Relation sensitivity – specificity:

Inverse:

increasing sensitivity will decrease specificity

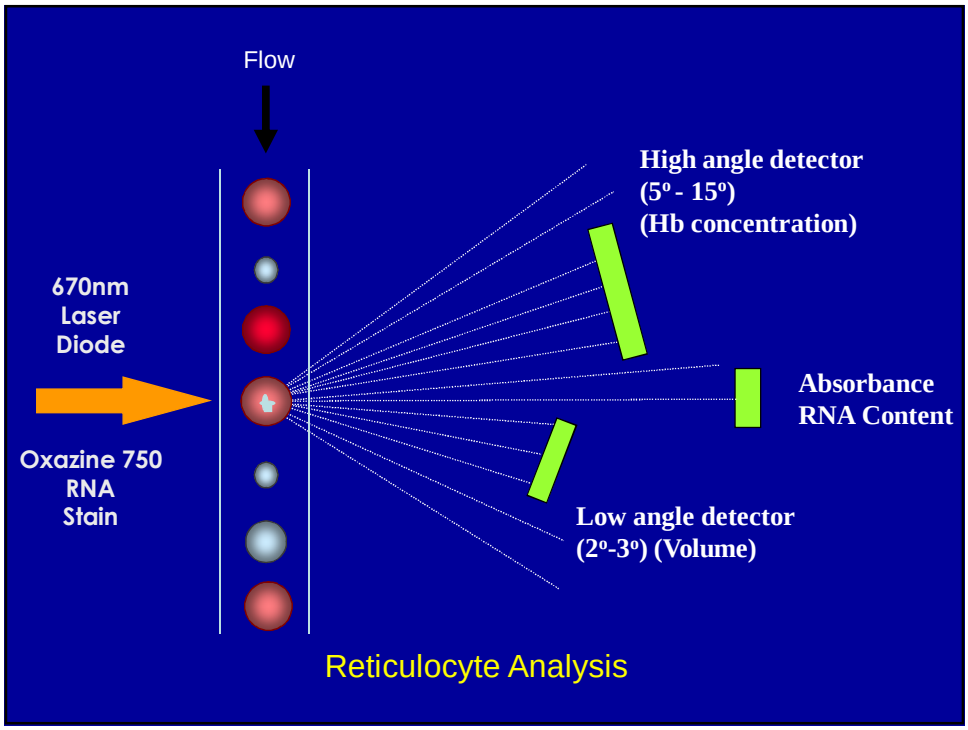
What is best cut-off point?

=> Use of Receiver Operating Characteristics (ROC) Curve

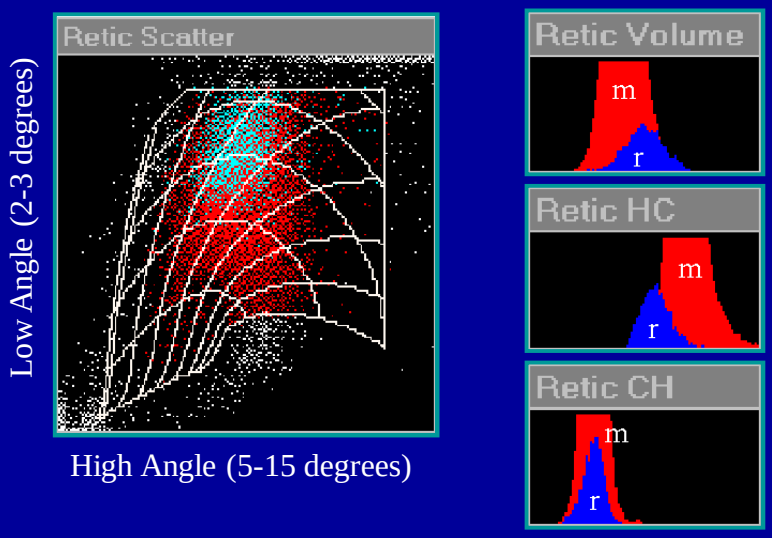


Receiver Operating Characteristics (ROC) Curve

ADVIA®2120
Hematology System



Reticulocyte Parameters



Example

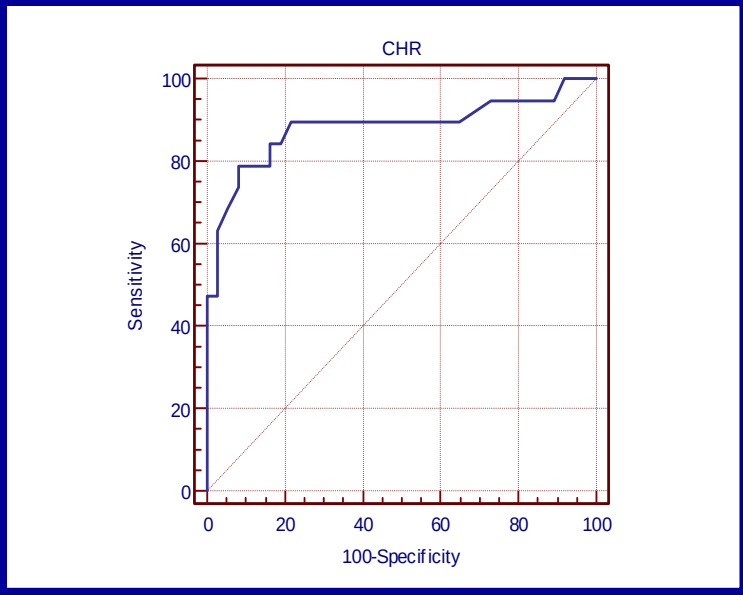
Iron deficiency is associated with decreased reticulocyte hemoglobin content (CHr)

Ref value CHr in dogs is 1.595 – 2.427 mmol/l

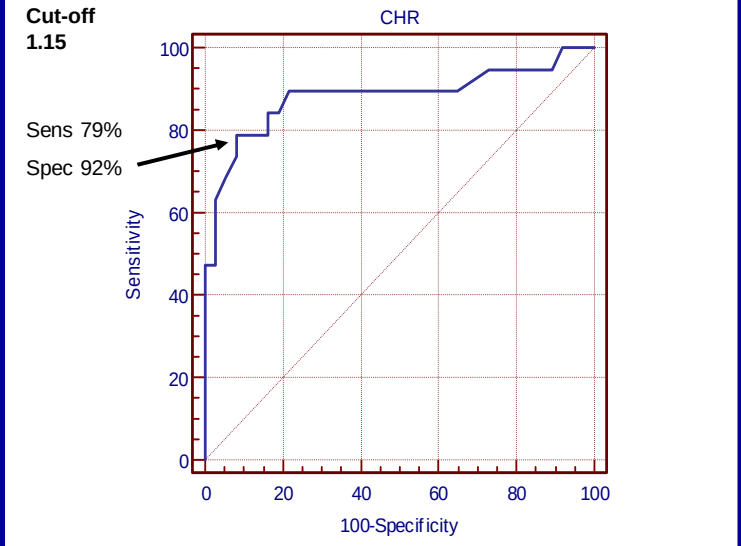
Study: group dogs with anaemia due to Fe def compared to group dogs with anaemia due to other reasons

Question: what is the best cut-off point for diagnosing Fe deficiency?

Criterion	Sens. (95% C.I.)	Spec. (95% C.I.)	+LR	-LR
< 0,89	0,0 (0,0- 17,8)	100,0 (90,4-100,0)		1,00
<=1,01	47,4 (24,5- 71,1)	100,0 (90,4-100,0)		0,53
<=1,04	47,4 (24,5- 71,1)	97,3 (85,8- 99,5)	17,53	0,54
<=1,12	63,2 (38,4- 83,6)	97,3 (85,8- 99,5)	23,37	0,38
<=1,13	68,4 (43,5- 87,3)	94,6 (81,8- 99,2)	12,66	0,33
<=1,14	73,7 (48,8- 90,8)	91,9 (78,1- 98,2)	9,09	0,29
<=1,15	78,9 (54,4- 93,8)	91,9 (78,1- 98,2)	9,74	0,23
<=1,26	78,9 (54,4- 93,8)	83,8 (68,0- 93,8)	4,87	0,25
<=1,28	84,2 (60,4- 96,4)	83,8 (68,0- 93,8)	5,19	0,19
<=1,32	84,2 (60,4- 96,4)	81,1 (64,8- 92,0)	4,45	0,19
<=1,33	89,5 (66,8- 98,4)	78,4 (61,8- 90,1)	4,14	0,13
<=1,56	89,5 (66,8- 98,4)	35,1 (20,2- 52,5)	1,38	0,30
<=1,57	94,7 (73,9- 99,1)	27,0 (13,8- 44,1)	1,30	0,19
<=1,75	94,7 (73,9- 99,1)	10,8 (3,1- 25,4)	1,06	0,49
<=1,77	100,0 (82,2-100,0)	8,1 (1,8- 21,9)	1,09	0,00
<=2	100,0 (82,2-100,0)	0,0 (0,0- 9,6)	1,00	



ROC curve



ROC curve

Criterion	Sens. (95% C.I.)	Spec. (95% C.I.)	+LR	-LR
< 0,89	0,0 (0,0- 17,8)	100,0 (90,4-100,0)		1,00
<=1,01	47,4 (24,5- 71,1)	100,0 (90,4-100,0)		0,53
<=1,04	47,4 (24,5- 71,1)	97,3 (85,8- 99,5)	17,53	0,54
<=1,12	63,2 (38,4- 83,6)	97,3 (85,8- 99,5)	23,37	0,38
<=1,13	68,4 (43,5- 87,3)	94,6 (81,8- 99,2)	12,66	0,33
<=1,14	73,7 (48,8- 90,8)	91,9 (78,1- 98,2)	9,09	0,29
<=1,15 *	78,9 (54,4- 93,8)	91,9 (78,1- 98,2)	9,74	0,23
<=1,26	78,9 (54,4- 93,8)	83,8 (68,0- 93,8)	4,87	0,25
<=1,28	84,2 (60,4- 96,4)	83,8 (68,0- 93,8)	5,19	0,19
<=1,32	84,2 (60,4- 96,4)	81,1 (64,8- 92,0)	4,45	0,19
<=1,33	89,5 (66,8- 98,4)	78,4 (61,8- 90,1)	4,14	0,13
<=1,56	89,5 (66,8- 98,4)	35,1 (20,2- 52,5)	1,38	0,30
<=1,57	94,7 (73,9- 99,1)	27,0 (13,8- 44,1)	1,30	0,19
<=1,75	94,7 (73,9- 99,1)	10,8 (3,1- 25,4)	1,06	0,49
<=1,77	100,0 (82,2-100,0)	8,1 (1,8- 21,9)	1,09	0,00
<=2	100,0 (82,2-100,0)	0,0 (0,0- 9,6)	1,00	

Conclusions

- Ref value CHr is 1.595 – 2.427 mmol/l
- As test to detect Relative Iron defeciency as cause of non-regenerative anemia:
  - For cut-off <1.15 mmol/l
    - Sensitivity is 79% (95% CI 64,4-93.8)
    - Specificity is 92% (95% CI 78.1-98.2)

Table 3. Statistical evaluation of the measured CEA and CA 15-3 values in clinically healthy bitches and bitches with mammary gland tumour

	CEA		CA 15-3	
	Healthy bitches	**Diseased bitches**	**Healthy bitches**	**Diseased bitches**
Minimum	0.1300	0.1800	3.020	7.100
Maximum	0.2300	0.4200	7.700	11.20
Mean	0.1955	0.2538 *	5.138	8.577 *
SD	0.03137	0.05671	1.339	1.270
95% Percentile	0.2295	0.4025	6.790	11.19
Cut off values	0.20-0.23		5.0-7.0	

- *: P<0.001
- Sensitivity for *CEA* to detect mammary carcinoma 60% and for *CA 15-3* 100%; specificity both 95%
- ET: not tested in benign tumours!!!!!!!
- ET: Cut-off values a range, not a calculated single value! (Due to column statistics?)

Making ROC curve

- Based on data in Table 1 and 2
- Put into Excel file
- Calculate ROC curves with statistical programme like MedCalc or Analyse-IT

Variable	CEA
Classification variable	Malignant

Sample size	45
Positive group : Malignant = 1	25
Negative group : Malignant = 0	20

Disease prevalence (%)	unknown

Area under the ROC curve (AUC)	0,868
Standard Error [a]	0,0517
95% Confidence Interval [b]	0,734 to 0,950
z statistic	7,122
Significance level P (Area=0.5)	0,0001

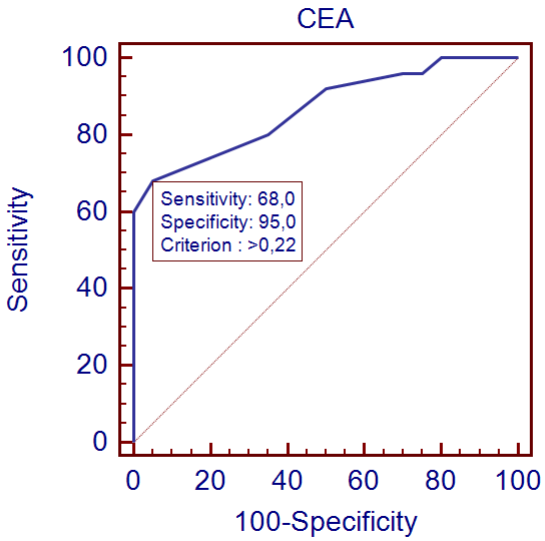
[a] DeLong et al., 1988

[b] Binomial exact

Criterion values and coordinates of the ROC curve [Hide]

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
>=0,13	100,00	86,3 - 100,0	0,00	0,0 - 16,8	1,00	
>0,16	100,00	86,3 - 100,0	20,00	5,7 - 43,7	1,25	0,00
>0,18	96,00	79,6 - 99,9	25,00	8,7 - 49,1	1,28	0,16
>0,19	96,00	79,6 - 99,9	30,00	11,9 - 54,3	1,37	0,13
>0,2	92,00	74,0 - 99,0	50,00	27,2 - 72,8	1,84	0,16
>0,21	80,00	59,3 - 93,2	65,00	40,8 - 84,6	2,29	0,31
>0,22 *	68,00	46,5 - 85,1	95,00	75,1 - 99,9	13,60	0,34
>0,23	60,00	38,7 - 78,9	100,00	83,2 - 100,0		0,40
>1,46	0,00	0,0 - 13,7	100,00	83,2 - 100,0		1,00

Data of Table 1 and Table 2 of VCO article used to make ROC curve



Variable	CA15_3 CA15-3
Classification variable	Malignant

Sample size		45
Positive group :	Malignant = 1	25
Negative group :	Malignant = 0	20

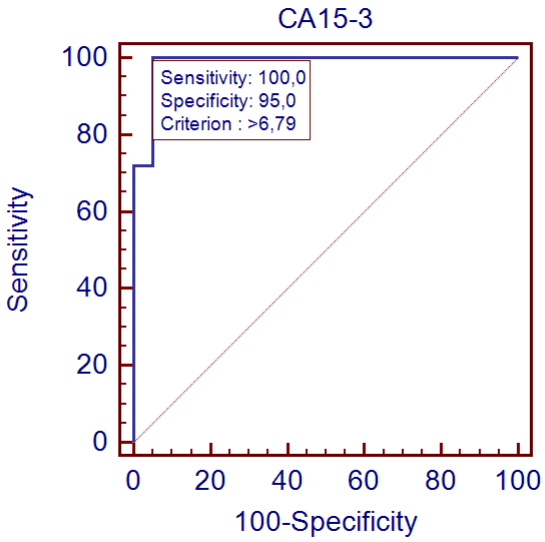
Disease prevalence (%)	unknown

Area under the ROC curve (AUC)	0,986
Standard Error [a]	0,0147
95% Confidence Interval [b]	0,896 to 1,000
z statistic	32,992
Significance level P (Area=0.5)	0,0001

[a] DeLong et al., 1988
[b] Binomial exact

Criterion values and coordinates of the ROC curve [Hide]

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
>=3,02	100,00	86,3 - 100,0	0,00	0,0 - 16,8	1,00	
>6,79 *	100,00	86,3 - 100,0	95,00	75,1 - 99,9	20,00	0,00
>7,67	72,00	50,6 - 87,9	95,00	75,1 - 99,9	14,40	0,29
>7,7	72,00	50,6 - 87,9	100,00	83,2 - 100,0		0,28
>11,2	0,00	0,0 - 13,7	100,00	83,2 - 100,0		1,00



Concurrent study

J Vet Intern Med 2012;26:1383–1388

CA15.3, CEA, and LDH in Dogs with Malignant Mammary Tumors

L.C. Campos, G.E. Lavalle, A. Estrela-Lima, J.C. Melgaço de Faria, J.E. Guimarães, Á.P. Dutra, E. Ferreira, L.P. de Sousa, É.M.L. Rabelo, A.F.D. Vieira da Costa, and G.D. Cassali

Table 2. CEA and CA15.3 serum levels in female dogs from groups I, II, III, and IV (mean, SD).

Group (n)	CEA (ng/mL)	CA15.3 (ng/mL)
Group I (30)	0.19 ± 0.20 [a]	1.19 ± 0.51 [a]
Group II (40)	0.12 ± 0.12 [a]	1.61 ± 0.61 [b]
Group III (12)	0.29 ± 0.36 [a]	2.39 ± 1.02 [c]
Group IV (8)	0.07 ± 0.04 [a]	2.46 ± 1.00 [c]

P<0.05 compared to I and II

The means followed by different letters in the same column differ statistically with *P*-value < .05. Group I: female dogs without mammary cancer; group II: female dogs with mammary cancer without metastasis; group III: female dogs with regional metastasis; group IV: female dogs with nonregional lymph node(s) metastasis.

Journal of Veterinary Internal Medicine
Volume 26, Issue 6, pages 1383-1388, 1 NOV 2012 DOI: 10.1111/j.1939-1676.2012.01014.x
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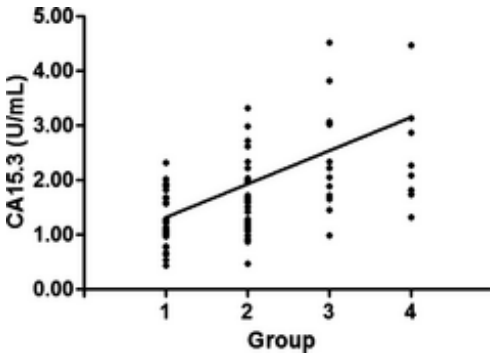
CA15.3 in Dogs with Malignant Mammary Tumors



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Veterinary and Comparative Oncology

Original Article

DOI: 10.1111/j.1476-5829.2012.00333.x

Diagnostic accuracy of pre-treatment biopsy for grading soft tissue sarcomas in dogs

Abstract

Histologic grade is an important prognostic factor for both local recurrence and metastatic potential with canine soft tissue sarcoma (STS). Pre-treatment biopsy with identification of tumour grade may aid in prognostication and determination of surgical margins necessary for local control. The purpose of this study was to evaluate the grading accuracy of various pre-treatment biopsy techniques (wedge, punch, needle-core) for STS in dogs. Medical records of 68 dogs diagnosed with a STS via pre-treatment biopsy and confirmed by excisional biopsy were evaluated. The concordance in grade between excisional and pre-treatment biopsies was 59%. Of the 41% that lacked concordance, 29% of pre-treatment biopsies underestimated and 12% overestimated grade. The method of pre-treatment biopsy did not significantly effect grade concordance. Based on these data, needle-core biopsy appears to be similar in accuracy compared to open biopsy, however, grading determined by pre-treatment biopsy in general should be interpreted with caution.

Hypotheses

- Concordance between the grade of pre-treatment and excisional biopsies regardless of tumour location, time interval between biopsy and excision?
- Larger biopsy samples (i.e. wedge biopsies) provide a more accurate means of determining tumour grade relative to less invasive (needle core, punch biopsy) techniques?

M&M

- Retrospective study
- Dogs with STS
- Both presurgical biopsy (needle or punch or wedge) and postsurgical histology (excisional)
- Graded I-III
- 70 dogs
- Evaluation by same (18%) or different pathologist (82%)!

Table 1. Adequacy and accuracy of various pre-treatment biopsy techniques compared to the gold standard (excisional biopsy)

	Needle core	Punch	Wedge
n	19	7	44
Adequate (%)	100	100	95
Accuracy (%)	58	57	61

In text 42 wedge biopsies

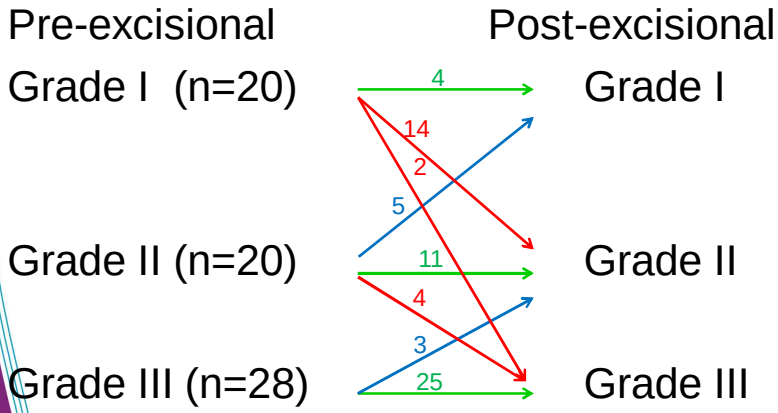
There was no statistical difference in the grading accuracy between these biopsy techniques.

Applies for Three-tier grading!

Twenty of the 68 (29%) pre-treatment biopsies underestimated the grade; 14/20 (70%) pre-treatment biopsies recorded as grade I were determined to be grade II on final histopathology (of excisional biopsy sample); 4/20 (20%) pre-treatment biopsies recorded as grade II were determined to be grade III on final histopathology; and 2/20 (10%) pre-treatment biopsies recorded as grade I were determined to be grade III on final histopathology. Eight of 68 (12%) pre-treatment biopsies overestimated the grade; 5/8 (63%) recorded as grade II were determined to be grade I on final histopathology and 3/8 (38%) recorded as grade III were determined to be grade II on final histopathology. Using the two-tier grading

?

Three-tier grading system



Discordance 41%

For Two-tier grading:

Table 2. Contingency table (A); and discordance, proportion of pre-treatment biopsies that overestimated grade, proportion of pre-treatment biopsies that underestimated grade, and Kappa statistic for pre-treatment biopsy versus excisional biopsy stratified by biopsy type (B)

Pre-treatment biopsy	Excisional biopsy	Tru-Cut ($n=19$)	Punch ($n=7$)	Wedge ($n=42$)	All ($n=68$)
A					
High grade	High grade	0	0	3	3
High grade	Low grade	1	0	2	3
Low grade	High grade	2	1	3	6
Low grade	Low grade	16	6	34	56
B					
		Tru-Cut $n=19$	Punch $n=7$	Wedge $n=42$	All $n=68$ (95% CI)
Discordance		16%	14%	12%	13% (7–23%)
Proportion of discordant results that overestimate grade		5%	0%	5%	4%
Proportion of discordant results that underestimate grade		11%	14%	7%	9%
Kappa statistic		−0.08	NA	0.48	0.33 (0.0–0.66)

Discordance 13%; No difference if one pathologist or two pathologists evaluated the two biopsies

What is Kappa statistics?

Reliability

In the absence of a ‘Gold’ standard:

- Agreement with other tests
- Repeatability / test – retest agreement
  - intra-observer variability
  - inter-observer variability

Set # 1

	Pathologist B		
Pathologist A	Tumour Positive	Tumour Negative	Total
Tumour positive	2	7	9
Tumour negative	3	88	91
Total	5	95	100

Observed agreement: (88+2)/100 x 100% = 90%

Set #2

	Pathologist B		
Pathologist A	Tumour Positive	Tumour Negative	Total
Tumour positive	40	6	46
Tumour negative	12	42	54
Total	52	48	100

Observed agreement: (40+42)/100 x 100% = 82%

Pathologists in Set #1 better than Pathologists in Set #2?

Set #1

	Pathologist B		
Pathologist A	Tumour Positive	Tumour Negative	Total
Tumour positive			9
Tumour negative			91
Total	5	95	100

Chance agreement:

Set #1

	Pathologist B		
Pathologist A	Tumour Positive	Tumour Negative	Total
Tumour positive	(5%x9%)x100 0.45	(95%x9%)x100 8.55	9
Tumour negative	(5%x91%)x100 4.55	(95%x91%)x100 86.45	91
Total	5	95	100

Chance agreement:

Set #1

	Pathologist B		
Pathologist A	Tumour Positive	Tumour Negative	Total
Tumour positive	(5%x9%)x100 0.45	(95%x9%)x100 8.55	9
Tumour negative	(5%x91%)x100 4.55	(95%x91%)x100 86.45	91
Total	5	95	100

Chance agreement: (0.45+86.45)/100 x 100% = 86.9%

Set #2

	Pathologist B		
Pathologist A	Tumour Positive	Tumour Negative	Total
Tumour positive			46
Tumour negative			54
Total	52	48	100

Chance agreement:

Set #2

	Pathologist B		
Pathologist A	Tumour Positive	Tumour Negative	Total
Tumour positive	(52%x46%)x100 =23.9	(48%x46%)x100 =22.1	46
Tumour negative	(52%x54%)x100 =28.1	(48%x54%)x100 =25.9	54
Total	52	48	100

Chance agreement:

Set #2

	Pathologist B		
Pathologist A	Tumour Positive	Tumour Negative	Total
Tumour positive	(52%x46%)x100 =23.9	(48%x46%)x100 =22.1	46
Tumour negative	(52%x54%)x100 =28.1	(48%x54%)x100 =25.9	54
Total	52	48	100

Chance agreement: (23.9+25.9)/100 x 100% = 49.8%

Kappa

Indicates the degree of agreement between two or more tests, excluding chance agreement

$$\text{Kappa} = (P_{observed} - P_{chance})/(1-P_{chance})$$

Kappa Set #1:

$(P_{obs} - P_{cha})/(100-P_{cha}) =$

$(90 - 86,9)/13.1 = 3.1/13.1 = 0.237$

Kappa Set #2:

$(P_{obs} - P_{cha})/(100-P_{cha}) =$

$(82 - 49,8)/50,2 = 32.2/50,2 = 0.641$

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Pre-treatment Biopsy	Excisional Biopsy		
	High Grade	Low Grade	
High Grade	3	3	6
Low Grade	6	56	62
	9	59	68

Kappa:

$(P_{obs} - P_{cha})/(100-P_{cha}) =$
$(86,7 - 80,3)/19,7 = 0.325$ (=poor)
Kappa: 0.33 (95%CI: 0.0-0.66)

Landis and Koch:

Kappa < 0.4: poor
Kappa 0.4-0.6: moderate
Kappa 0.6-0.8: good
Kappa >0.8: excellent

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Pre-treatment Biopsy	Excisional Biopsy		
	High Grade	Low Grade	
High Grade	3	3	6
Low Grade	6	56	62
	9	59	68

Sensitivity for detecting HG lesions: 3/9 = 33%
Specificity: 56/59= 95%

Discussion: "A diagnosis of high grade can be believed but a diagnosis of low grade cannot"

However: Pos Pred Val = 50% and Neg Pred Val= 90.3% !

Veterinary and Comparative Oncology
Original Article
Diagnostic accuracy of pre-treatment biopsy for grading soft tissue sarcomas in dogs

Discussion

- Discordance 13%; No difference if one pathologist or two pathologists evaluated the two biopsies
- Regan et al: 12% discordance for evaluating subtypes of STS and 17% for grading
- Coindre et al (human study): 25% discrepancy in grade

Regan/Coindre studies:
No mentioning of frequency of categories. Therefore, just chance agreement, no Kappa

Efficacy of systemic adjuvant therapies administered to dogs after excision of oral malignant melanomas: 151 cases (2001–2012)

SMALL ANIMALS/ EXOTIC

Objective—To determine prognostic factors for and compare outcome among dogs with oral malignant melanoma following excision with or without various systemic adjuvant therapies.

Design—Retrospective case series.

Animals—151 dogs with naturally occurring oral malignant melanomas treated by excision with or without adjuvant therapies from 2001 to 2012.

Procedures—Case accrual was solicited from Veterinary Society of Surgical Oncology members via an email list service. Information collected from case records included signalment, tumor staging, tumor characteristics, type of surgical excision, histologic diagnosis, adjuvant therapy, and survival time.

Results—The overall median survival time was 346 days. Results of multivariate analysis indicated that tumor size, patient age, and intralesional excision (vs marginal, wide, or radical excision) were considered poor prognostic indicators. All other demographic and clinical variables were not significantly associated with survival time after adjusting for the aforementioned 3 variables. A clear survival benefit was not evident with any systemic adjuvant therapy, including vaccination against melanoma or chemotherapy; however, the number of dogs in each treatment group was small. Ninety-eight dogs received no postoperative adjuvant therapy, and there was no difference in survival time between dogs that did (335 days) and did not (352 days) receive systemic adjuvant therapy.

Conclusions and Clinical Relevance—For dogs with oral malignant melanoma, increasing tumor size and age were negative prognostic factors. Complete excision of all macroscopic tumor burden improved survival time. Long-term survival was possible following surgery alone. Although systemic adjuvant therapy was not found to improve survival time, this could have been due to type II error. (*J Am Vet Med Assoc* 2014;245:401–407)

Efficacy of systemic adjuvant therapies administered to dogs after excision of oral malignant melanomas: 151 cases (2001–2012)

SMALL ANIMALS/ EXOTIC

- AIM:
  - To determine prognostic factors
  - To compare outcomes between surgery alone and surgery + systemic adjuvant therapies

RETROSPECTIVE MULTICENTERS STUDY

Materials and Methods

- Dogs (2001-2012):
  - Oral malignant melanoma confirmed by histology
  - Signalement, tumor size, location, metastases
  - Type of excision, margins
  - Adjuvant radiation therapy, systemic adjuvant therapy (chemo/TKI's/Melanoma Vaccine)
  - Type of excision

Materials and Methods

- Type of excision:
  - Intralesional excision: excision within the tumor with cytoreductive intent
  - Marginal excision: apparent removal of all macroscopically tumor tissue but with margin within the tumor reactive zone
  - Wide excision: margin outside the tumor reactive zone
  - Radical excision: removal of an anatomic segment with margin outside the reactive zone

Materials and Methods

- Statistics:
  - OST compared by log rank
  - Hazard ratio's + 95%CI by Cox proportional hazard regression model
  - Forward selection method
  - No mentioning of censoring!
  - Receiver Operating Characteristic curve analysis of age-effect on mortality (determining cut-off value)

RESULTS

- 151 dogs
  - 8 institutions, 4 countries
  - Median age: 12 years (4.7 to 17.8 years)
  - Median weight: 22.3 kg (2.3 to 69 kg)
  - Cocker, labrador, retriever

RESULTS

- Tumor location
  - Mandible : 38%
  - Maxilla : 27%
  - Lip: 23%
  - Palate: 5%
  - Other: 6%

50% as a left position
39% as a right position
11% as a central position

64% rostrale
36% caudale

- Tumor size
  - Median: 2.6 cm (0.4 to 7 cm)
    - 29% <2cm
    - 53% 2-4 cm
    - 19% > 4 cm

RESULTS: Tumor staging

- Mandibular lymph nodes

	Se	Sp	PPV	NPV
Palpation	65.6%	77.8%	84%	56%
Cytology	78.1%	64.3%	83.3%	56.3%

- Thoracic XR (in 127/151 dogs):
  - 122 dogs -
  - 2 dogs +
  - 3 dogs equivocal

?

- Thoracic CT (in 18/151 dogs):
  - 14 dogs –
  - 3 dogs + (2 XR – et 1 XR equivocal)
  - 1 dog equivocal

Discussion

- *Given the low sensitivity and specificity of both lymph node palpation and cytologic evaluation for detection of metastatic disease in dogs with oral malignant melanoma in the present study, routine (histologic) biopsy of lymph nodes is recommended for lymph node staging.*

- Unexpected low accuracy for cytology
- Not much known in other studies in veterinary medicine
- What is known in human medicine? => literature search

Fine-Needle Aspiration Cytology for the Diagnosis of Metastatic Melanoma

Systematic Review and Meta-Analysis

Brian J. Hall, MD,[1] Robert L. Schmidt, MD, PhD, MBA,[1] Rohit R. Sharma, MD,[2] and Lester J. Layfield, MD[1]

From the [1]Department of Pathology, University of Utah School of Medicine, Salt Lake City; and [2]Department of Surgery, University of Texas Southwestern Medical School, Dallas.

Key Words: Melanoma; Metastatic melanoma; AP cytopathology; Fine-needle aspiration; Meta-analysis; Systematic review; Surgical oncology

DOI: 10.1309/AJCPWSDDHLLW40WI

CME/SAM

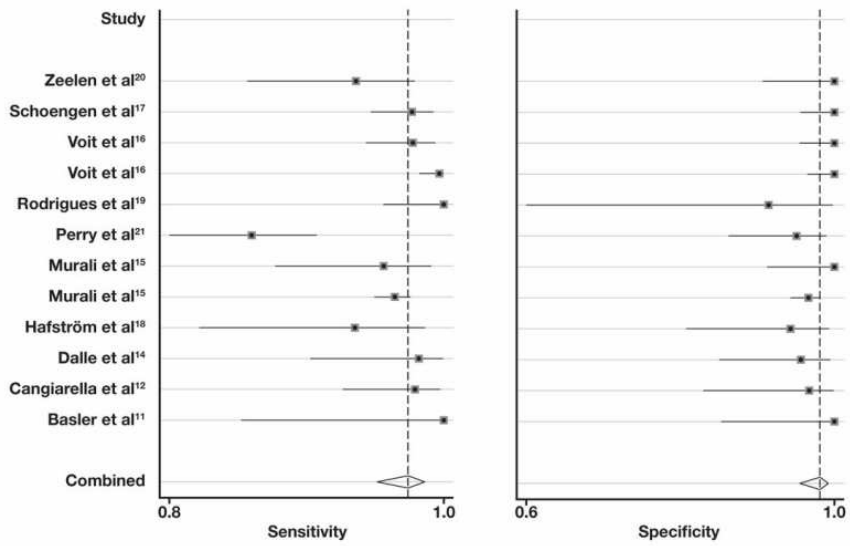
ABSTRACT

Objectives: *To perform a thorough review and meta-analysis of studies that have shown non–image-guided fine-needle aspiration cytology (FNAC) to be highly sensitive and specific for assessing questionable metastatic melanoma to lymph nodes.*

Methods: *MEDLINE and Scopus were searched for potentially relevant articles with a search string including the words "melanoma" and "fine needle." All relevant articles were screened by two authors (B.J.H. and R.L.S.). Full articles were screened for extractable data, and the data was pooled for analysis.*

Conclusions: *With a sensitivity and specificity of 0.97 and 0.99, the overall diagnostic accuracy of FNAC for metastatic melanoma is quite high, and with a positive and negative likelihood ratio of 58 and 0.03, FNAC for metastatic melanoma should be the first-line option in a patient with a clinically suspected mass and a history of melanoma.*

Am J Clin Pathol 2013;140:635-642



Results Meta-anaylsis Hall et al, AM J Clin Pathol 2013

RESULTS: Surgery

- Type:
  - Intralesional: 7 dogs
  - Marginal: 29 dogs
  - Wide or radical: 114 dogs
  - Unknown: 1 dog
- Margins:
  - Complete excision: 77 dogs
  - Incomplete excision: 45 dogs
  - Unknown: 29 dogs

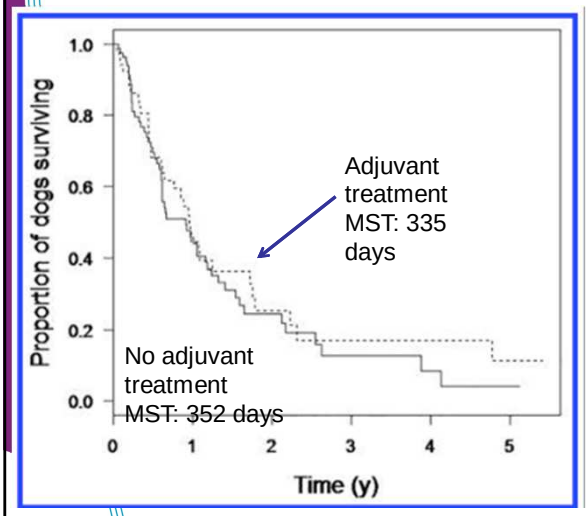
RESULTS: Adjuvant therapy

- No systemic adjuvant treatment: 98 dogs
- Radiation : 12 dogs
- Chemotherapy: 32 dogs
  - 26 dogs with platinum-based treatment (Carboplatin for 22 dogs)
  - Lomustine, darcabazine, doxorubicin
- Metronomic in 4 dogs
- Vaccine: 24 dogs
  - 14 commercial vaccine
  - 10 investigative vaccine (University of Wisconsin)

RESULTS

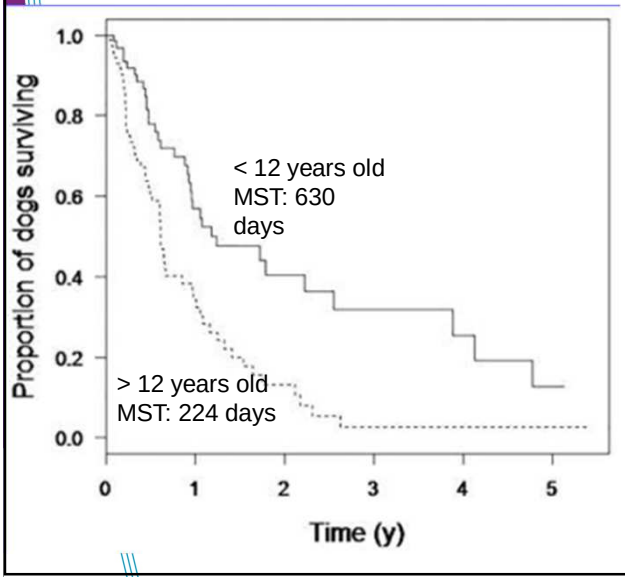
- Total amount of treatments: (98+12+32+4+24)=172! In 151 dogs!
- Means that there are double treatment modalities (even in addition to radiotherapy)

RESULTS



No significant improvement on the survival time with systemic adjuvant treatment

RESULTS



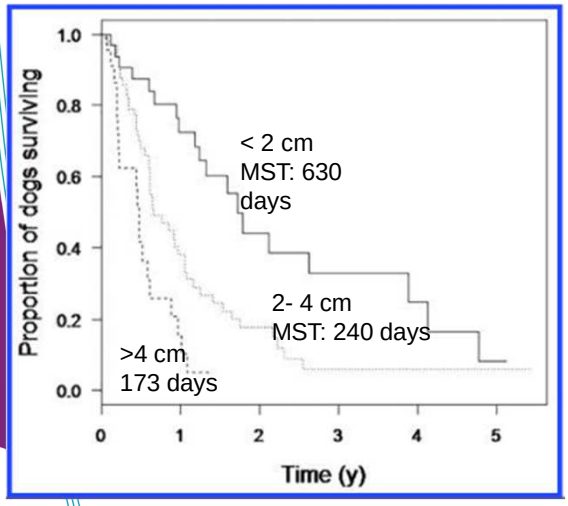
- Age > 12 years old is significantly associated with reduced survival time
- Bias?

Bias

- In Discussion:
  - *Older dogs were less likely to receive additional aggressive treatment?*
  - *Perhaps more often aggressive melanomas?*
- There was most likely no censoring: old dogs survive shorter than younger dogs!
- Systemic treatment reserved for worse cases?

Most likely biased outcome of age as prognosticator was listed in abstract without restraint!

RESULTS



Tumor size has a significant effect on survival time

RESULTS

- Intralesional incision had a negative impact on survival time : MST of 117 days
- No shorter MST with marginal excision
- Metronomic treatment had an increased hazard ratio (7.82; 95% CI 2.36-25.93;P=0.001)
- Radiation therapy HR of 0.20, but confounded by age (younger dogs more likely to have RT), in multivariate analysis it did not come out as significant.
- Multivariate analysis: factors: Age, tumor dimension, and type of excision.

LIMITATIONS

- HETEROGENOUS GROUPS !!!!
  - Some dogs received several adjuvant treatments
    - Radiotherapy + chemotheray
    - Chemotherapy + vaccine
    - Etc
- Low number of dogs in each groups
- Multicenter retrospective trial Different quality of clinicians/cytologists,
- No histologic informations (Grade (mitotic index, atypia…) is one of the most important prognostic factors)
- CRITERIA to choose palliative treatment?
  - Different centers so differents opinions → Bias selection

Remarkable facts from discussion

- Routine cytology not recommended
- Dissection of contralateral lymph node recommended: no data on frequency!
- Median OST 346 days; with 29% of dogs living >1 year: => means that between 346-365 days 21% of dogs die!!!!
- Post hoc analysis: low statistical power (13.5%)

J Vet Intern Med 2000;14:395–398

Canine Hemangiosarcoma Treated with Standard Chemotherapy and Minocycline

Standard treatments for canine hemangiosarcoma include surgery and chemotherapy with doxorubicin, but in spite of treatment most dogs with this disease die within 6 months of diagnosis. Tumor growth and metastasis are angiogenesis dependent. Antiangiogenic drugs such as minocycline may provide therapeutic benefits in cancer patients. The purpose of this prospective study was to evaluate the efficacy of chemotherapy with doxorubicin and minocycline, an antiangiogenic agent, in dogs with hemangiosarcoma. Eighteen dogs with histologically confirmed hemangiosarcoma of any stage were treated with doxorubicin, cyclophosphamide, and minocycline. Complete staging was performed before and during the treatment period to assess remission status and response to therapy. No statistically significant difference was found in survival between the dogs treated with chemotherapy and minocycline, and historical controls consisting of dogs that received chemotherapy alone. Postmortem examination revealed widespread metastasis, suggesting that minocycline is ineffective as a single antiangiogenic agent in canine hemangiosarcoma.

Key words: Angiogenesis; Antiangiogenic therapy; Malignant endothelioma; Metastasis.

J Vet Intern Med 2000;14:395–398
Canine Hemangiosarcoma Treated with Standard Chemotherapy and Minocycline

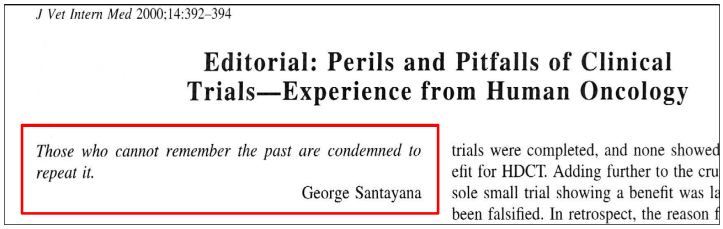
Abstract:

[…] Tumor growth and metastasis are angiogenesis dependent. Antiangiogenic drugs such as minocycline may provide therapeutic benefits in cancer patients. The purpose of this prospective study was to evaluate the efficacy of chemotherapy with doxorubicin and minocycline, an antiangiogenic agent, in dogs with hemangiosarcoma. Eighteen dogs […] were treated with doxorubicin, cyclophosphamide, and minocycline.
No statistically significant difference was found in survival between the dogs treated with chemotherapy and minocycline, and historical controls consisting of dogs that received chemotherapy alone. Postmortem examination […] minocycline is ineffective as a single antiangiogenic agent in canine hemangiosarcoma.

J Vet Intern Med 2000;14:395–398
Canine Hemangiosarcoma Treated with Standard Chemotherapy and Minocycline
Karin Sorenmo, Lili Duda, Lisa Barber, Kim Cronin, Carl Sammarco, Amy Usborne, Michael Goldschmidt, and Frances Shofer

However, in Discussion it is stated:

"This may be due to the relatively low numbers of dogs in each stage category and the wide range of survival within each stage.[28] In order to detect a difference of magnitude of 1-month survival between treatments, with a power of 80% and alpha of 0.05, one would need 50 patients in each treatment arm. With the current sample size of 17 and 16, power was reduced to 30%."



J Vet Intern Med 2000;14:392–394

Editorial: Perils and Pitfalls of Clinical Trials—Experience from Human Oncology

Those who cannot remember the past are condemned to repeat it.

George Santayana

trials were completed, and none showed
efit for HDCT. Adding further to the cru
sole small trial showing a benefit was la
been falsified. In retrospect, the reason f

"Many studies contain too few patients to achieve the stated aims of the trial. If the statistical power of the study is too low, then a negative result may simply be due to an insufficient number of patients to provide a statistically significant answer. For this reason, a negative underpowered study actually provides no real answers."

Statistical power

The power of a test is the probability that a given test will find an effect assuming that one exists in the population. […] We should aim to achieve a power of 0,8 or an 80% change of detecting an effect if one genuinely exist.

A. Field, Discovering Statistics Using SPSS, 2005

So, with a power of 30% there is a (100-30=)70% chance to find no effect, when in reality there is an effect.

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Canine Hemangiosarcoma Treated with Standard Chemotherapy and Minocycline

Karin Sorenmo, Lili Duda, Lisa Barber, Kim Cronin, Carl Sammarco, Amy Usborne, Michael Goldschmidt, and Frances Shofer

1. 18 dogs with HSA treated with doxorubicine + cyclophosphamide and an angiogenesis inhibitor (minocycline)
2. No improvement compared to historical group dogs treated with DOX+CTX (J Vet Intern Med 1993)
3. Stage I a little bit better prognosis (P=0.135) by higher effectivity chemo+Minocycline?

Outcome (remarks)

- Historical control group
- No phase 1 and phase 2 results of Minocycline known
- Correct dosage? Maasland et al, Vet Dermatol 2014: based on pharmacokinetics and –dynamics: dosage recommendation 5mg/kg orally TWICE a day.
- Different types of HSA (10x spleen; 5x subcutaneous; 2x multicentric; 1x retroperitoneal)
- No censoring in survival analysis (2 dogs not tumor related death);
- Stage I somewhat longer survival with chemo and Minocycline compared to chemo alone?
  Effect different staging over time => Stage Migration

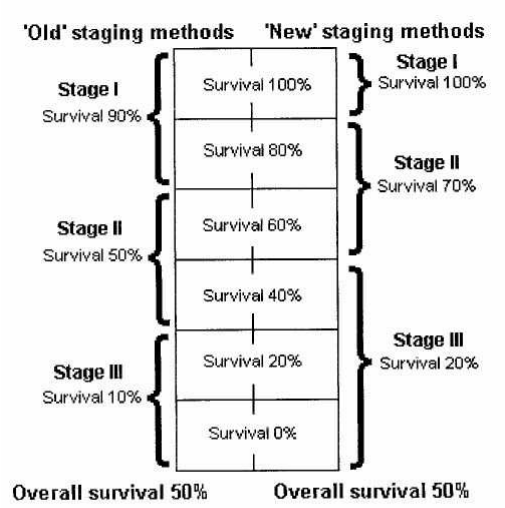

Fig 1. Illustration of stage migration. A theoretical cancer patient population is shown in the boxes, with a survival figure for each group of patients. To the left are the survivals for patients staged by the old methods, with an overall survival of 50%. The new staging methods on the right have shown improved survival for each stage by migrating patients from a lower stage to a higher stage. All stages show an improved survival, but the overall survival is unchanged (adapted from Tannock[3]).