POSTER
#PMU4

WHAT IS A GOOD OR BAD NUMBER NEEDED TO TREAT (NNT) VALUE? A LITERATURE REVIEW

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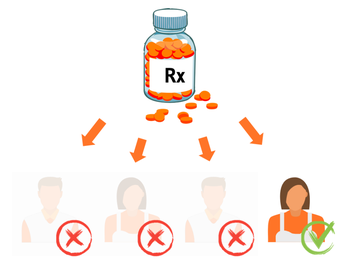
PURPLE SQUIRREL ECONOMICS

BACKGROUND

- The NNT is the result of comparison between two treatments and usually is calculated using the inverse of the absolute risk reduction (Laupacis et al. 1988 and Cook et al. 1995), though it can be calculated from odds ratios (Guyot et al, 2018). It measures the effectiveness of an intervention through defining the number of patients that need to receive an active treatment, over a control, to observe the prevention of one additional adverse outcome or the acquisition of one additional beneficial outcome (Laupacis et al. 1988 and Cook et al. 1995).

$$NNT = \frac{1}{Control_i - Rx_i} = \frac{1}{\frac{8}{16} - \frac{4}{16}} = 4$$

$Rx_i = Incidence\ of\ adverse\ outcome\ in\ experimental\ Rx\ group$
$Control_i = Incidence\ of\ adverse\ outcome\ in\ control\ group$



- A perfect NNT would be 1, meaning that for every patient treated with a specific intervention in a study, we were able to observe a beneficial outcome. Seemingly, the larger the NNT, the fewer people benefit from the intervention. With respect to the field of oncology, no threshold is currently available for what can be considered an acceptable NNT. Not only does the use of NNT assist physicians in selecting the best treatment in daily clinical practice (Straus et al. 2011 and Citrome et al. 2013), but it has also been deemed valuable for decision making in drug regulation (Mendes et al. 2017).

OBJECTIVE

The goal of this review was to investigate the range and averages of reported NNT in selected oncology studies and examine the factors affecting NNT value in oncology.

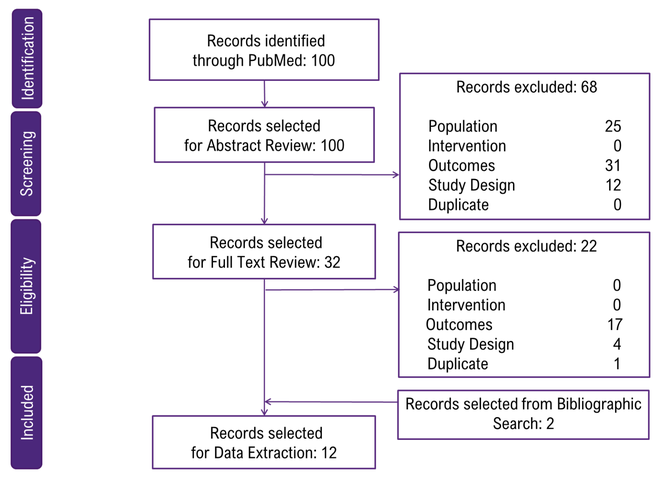
LITERATURE REVIEW

Table 1: PICOS used in the selection process

PICOS	Inclusion	Exclusion
Patient population	• Patients diagnosed with any type of cancer	• Patients without cancer • Patients diagnosed with cancer, but mixed with other diseases
Intervention and Comparators	• Not applicable	• Not applicable
Outcomes measures	• NNT reported for Overall Survival (OS) • NNT reported for Progression Free Survival (PFS) • NNT reported for reduction in risk of cancer mortality	• NNT reported for other outcomes except OS and PFS (e.g. EFS, DFS, CCR)
Study design	• Prospective observational studies • Retrospective studies • Interventional studies • Database analyses • Registries • Systematic reviews and meta-analyses • Pooled analyses	• Case reports • Notes/Comments/Letters • Non-human • Case series • Editorial • Review • Published studies before 2000

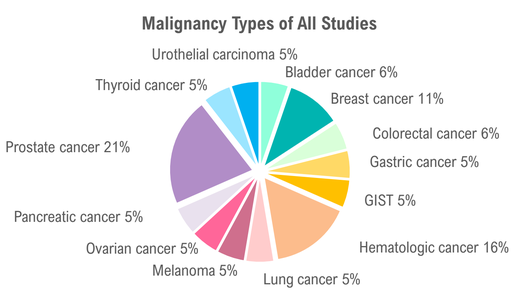
- A targeted literature search was conducted on June 5th, 2019 using the PubMed database, and NNT data from studies on different cancers were extracted.
- Details on inclusion and exclusion criteria are depicted in **Table 1**.
- Analysis of data was completed through average and distributional ranges to help determine the positioning of NNT values in published literature within the field of oncology.
- The results were evaluated and compared to identify factors influencing their values.
- 10 of the 100 studies initially identified and 2 additional studies identified through cross-checking met the inclusion criteria.

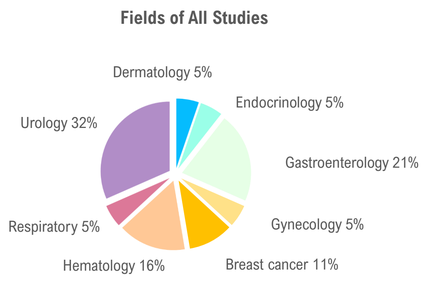
Figure 1: PRISMA



TRENDS IN PUBLISHED LITERATURE

- Of the reported NNT, 32% were in urologic cancers (mainly prostate cancer), followed by 21% in gastroenterological cancers (mainly gastrointestinal stromal tumors), 16% in hematologic cancers (mainly leukemia and lymphoma), 5% in gynecological cancers and 11% in breast cancer.





NNT RANGE IN ONCOLOGY

- In the oncology field, the overall range of NNT in all tumor types, all time frames and in all outcomes of interest to this review (PFS, OS, and reduction in mortality), ranged between –180 and 247. The observed mean was 24 and the median was 13.

Figure 2: Range of NNT in the field of oncology

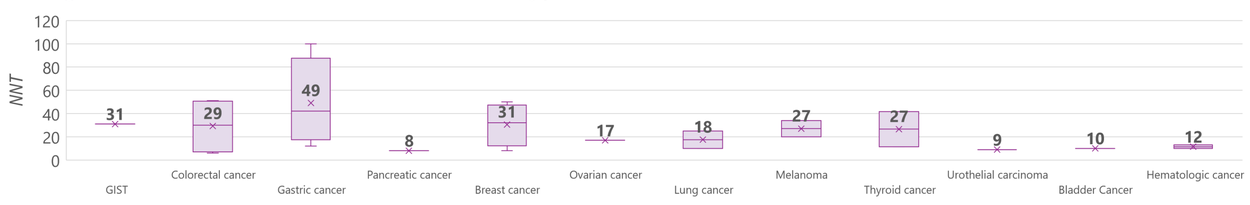
*In all tumor types, all interventions time frames; all outcomes of interest (PFS, OS, reduction in mortality); X : mean value

NNT IMPACTING FACTORS

1) UNDERLYING TUMOR TYPE

- The range of reported NNT values for OS varied widely: from 6 to 100, within the area of oncology and in a 1 to 3-year time frame. Depending on the specific oncology field, the mean of NNT varied between 10 (urologic cancers) and 35 (gastroenterological cancers).
- When comparing more specific tumor types, the range of reported NNT means is greater (from 8 in pancreatic cancer to 49 in gastric cancer).

Figure 3: NNT values in different tumor types*

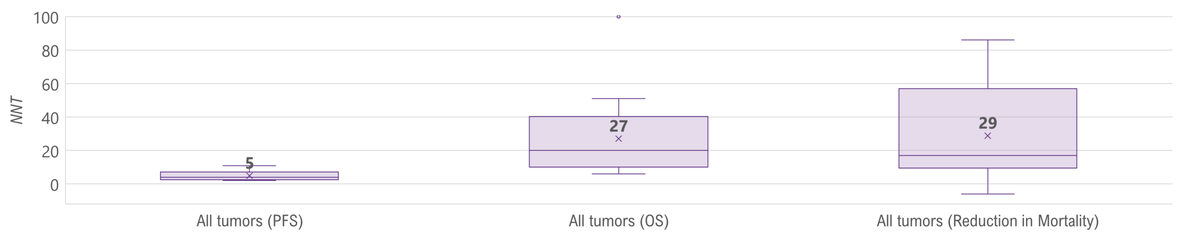


*With treatment as the intervention; with a follow-up of 1-3 years; with the OS outcome; X : mean value

2) TYPE OF OUTCOME

- The type of outcome for which an NNT value is reported can be an important influential factor for the NNT value. As observable in **Figure 4**, the range of reported NNT for PFS was narrow with a low mean of 4, but this range was wider for OS and reduction in mortality, where the mean of NNT could reach a value as high as 27 and 28, respectively.

Figure 4: Range of NNT for each outcome of interest*



*In all included studies; divided by outcome; X : mean value

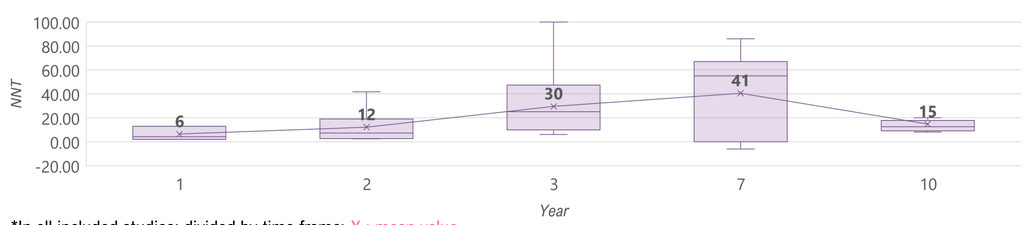
4) EXPERIMENTAL ARM AND COMPARATORS

- NNT being an incremental value comparing two interventions, undeniably both would play a significant role in impacting the calculated value. More than the intervention itself, the type of intervention can play a significant role.
- All included NNTs in this review are in the field of treatment, within which the highest reported value was 247. In comparison, Collins et al. 2008 reported an NNT value reaching up to 33,000 to prevent one death for the intervention of screening in prostate cancer.

5) TIME FRAME

- The timeframe of calculation can significantly affect NNT: results of this review show the cumulative average of NNT in included studies increased from 6 to 41 in the first 7 years, before decreasing to 15 in the following 3 years (**Figure 5**).

Figure 5: Range of NNT through time*



*In all included studies; divided by time frame; X : mean value

6) PATIENT CHARACTERISTICS

- Baseline patient characteristics also play an important role in impacting NNT. Greenberg et al. 2015 compared radical prostatectomy and radical radiotherapy in the treatment of prostate cancer. They observed a large variability in NNT values for reduction in risk of cancer mortality in isolated patient groups: an NNT of 247 was reported in patients under 60 with intermediate risk for primary non-metastatic prostate cancer, and a value of –180 for patients between 70-79 years of age with high risk for primary non-metastatic prostate cancer.

DISCUSSION & RECOMMENDATIONS

Whether the NNT value is acceptable is highly related to the outcome. While the mean of reported NNT for PFS was 4, it was 27 for OS and 28 for reduction in mortality. In other words, if a clinical endpoint is devastating enough (e.g. OS and reduction in mortality), treatment with a high NNT may still be indicated in such situations.

As previously discussed, the timeframe is critical for NNT and should be considered in meta-analysis. NNT values reported without their timeframe make for a difficult interpretation of results and weaken the data's comparability with other studies. A few studies, (eg, Gandaglia et al. 2014), provided p-values for the related HRs that were used to calculate NNT. This could be useful to interpret the NNT value and find an acceptable threshold.

While an acceptable NNT is usually considered as less than 10 (Citrome et al. 2013), the mean NNT reported in the field of oncology was 24 for the 3 outcomes of interest in this review (OS, PFS, reduction in mortality). A large variability was observed in the oncology-related NNTs. This variability leads to the conclusion that this type of value cannot be interpreted without considering a range of factors identified through this review, listed below. These factors are important and need to be clearly reported when stating NNT values.

1. Underlying disease and tumor types | **2. Outcome for which NNT is reported** | **3. Time frame** | **4. Type of intervention and comparator** | **5. Patient characteristics**

CONCLUSIONS

While the acceptable NNT in the field of oncology is higher than in other fields of treatment, it cannot be interpreted by its value alone. Its acceptance varies based on several factors that need to also be considered. This research provides the first review of reported NNT in the field of oncology to show the variability of NNT and the important factors that affect its final results.

OUR POSTER

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ISPOR EUROPE 2019 (Copenhagen)

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