

Long Term Effects of Using Medicinal Mushroom Preparations in Human Colorectal and Breast Cancer

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Purpose

- A longer time span analysis of a 2007 work “Effects of Using Medicinal Mushroom Preparations in Human Colorectal and Breast Cancer”
- 2008 Cancer **Incidence and Deaths**¹
Colorectal (3rd most common): 1.235.108 (609.051)
Breast (2nd most common): 1.384.155 (458.503)
- Effects of chemotherapy in these cancers: **useless or improves survival only slightly** (4% in colorectal, just 1.5% in breast cancer)^{2,3}
- Use of medicinal mushroom preparations against cancer, is scientifically justified, but **mostly unknown in the West**

1 Globocan 2008 (globocan.iarc.fr)

2 <http://www.coloncancerresource.com/colon-cancer-survival-statistics.html>

3 Morgan G, Ward R, Barton M (December 2004). "The contribution of cytotoxic chemotherapy to 5-year survival in adult malignancies". *Clin Oncol (R Coll Radiol)* 16 (8): 549-60. PMID 15630849

Methodology

- **demonstrational study** looking at effects of using medicinal mushroom extracts (MT) in adjuvant and as primary therapy
- **Consecutive sample** – general population of patients
 - starting treatment from January 2005 to January 2006
 - follow-up until end of December 2010
- Data sources: **official medical records, cancer registers**
- **Sample models** statistical properties of the general patient population well

Official therapy procedure (ST) done independently of mycotherapy (MT)

Therapeutic use of medicinal mushrooms

- Mycotherapy used: liquid form **extracts from a blend of medicinal mushrooms** (Lentifom – 3 species, Agarikon – 8 species, Agarikon Plus – 10 species) manufactured by **Dr Myko San – Health from Mushrooms**
- Lentifom is taken in quantities correlated with body weight
- Mushroom polysaccharides taken daily amount to approx. **0.1g/kg bodyweight/day**

Forte dosages used at the start of MT

(1 Forte dosage lasts 10 days)

- All participants in both samples took **at least 4 Forte dosage (40 days)**

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Colorectal cancer sample

- **Sample size: 52**
- Most fundamental division based on location: colon and rectal cancer

While we have looked at colorectal cancer as a single entity, for completeness we show some data separately

Colorectal cancer
Sample size: 52
Male/female: 24–28

Colon cancer
Sample size: 28
Male/female: 11–17

Rectal cancer
Sample size: 24
Male/female: 13–11

Official general population

Male to female ratio: colon cancer more frequent in females, rectal in males

Sample starting oncologic status

- The main difference to the general population of patients (significant negative skew)
- **More ARM cases** (advanced, recurrent, metastatic) in sample

Chemotherapy was found to be more useful for small tumors, so this sample is less influenced by chemotherapy

More complex cases may be the result of generally unknown and un-established method of using medicinal mushrooms in cancer treatment

Sample starting oncologic status (cont'd)

The TNM distribution of the sample shows very difficult cases

- 68% of sample are Stage 4 (most difficult stage, distant metastases present); 5–Y survival rate for this group is 5–8%

Average stage: 3.6

TNM stage	Total	Colon	Rectal
I	1	0	1
II A	1	0	1
II B	1	0	1
III A	1	0	1
III B	5	4	1
III C	7	3	4
IV	34	19	15

Sample starting oncologic status (cont'd)

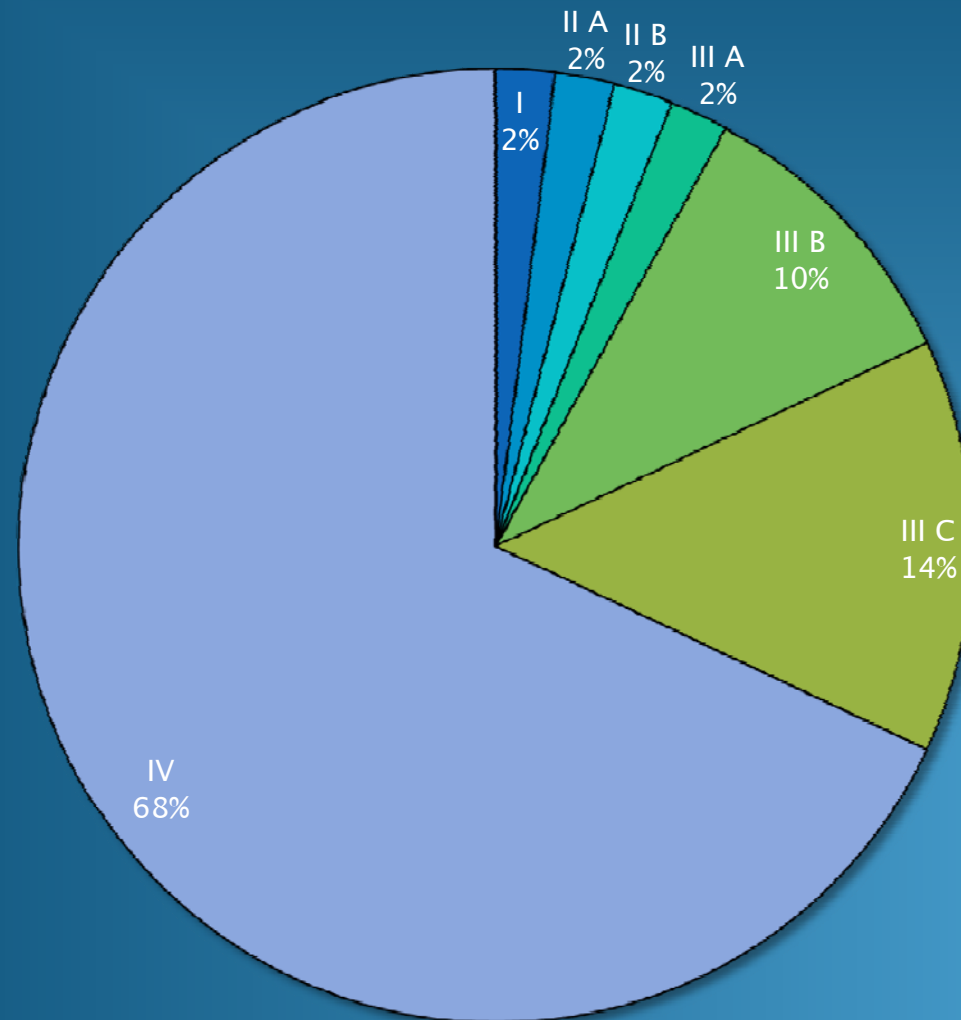
Disproportionally large number of surgically unresected and metastatic cases

Status	Total	Colon	Rectal
Resected	17	9	8
Unresectable, residual	1	0	1
Resected w/meta	4	4	0
Unresected w/meta	30 ¹	15	15

1 Patients with surgically inoperable, metastatic cancers have an especially bad prognosis

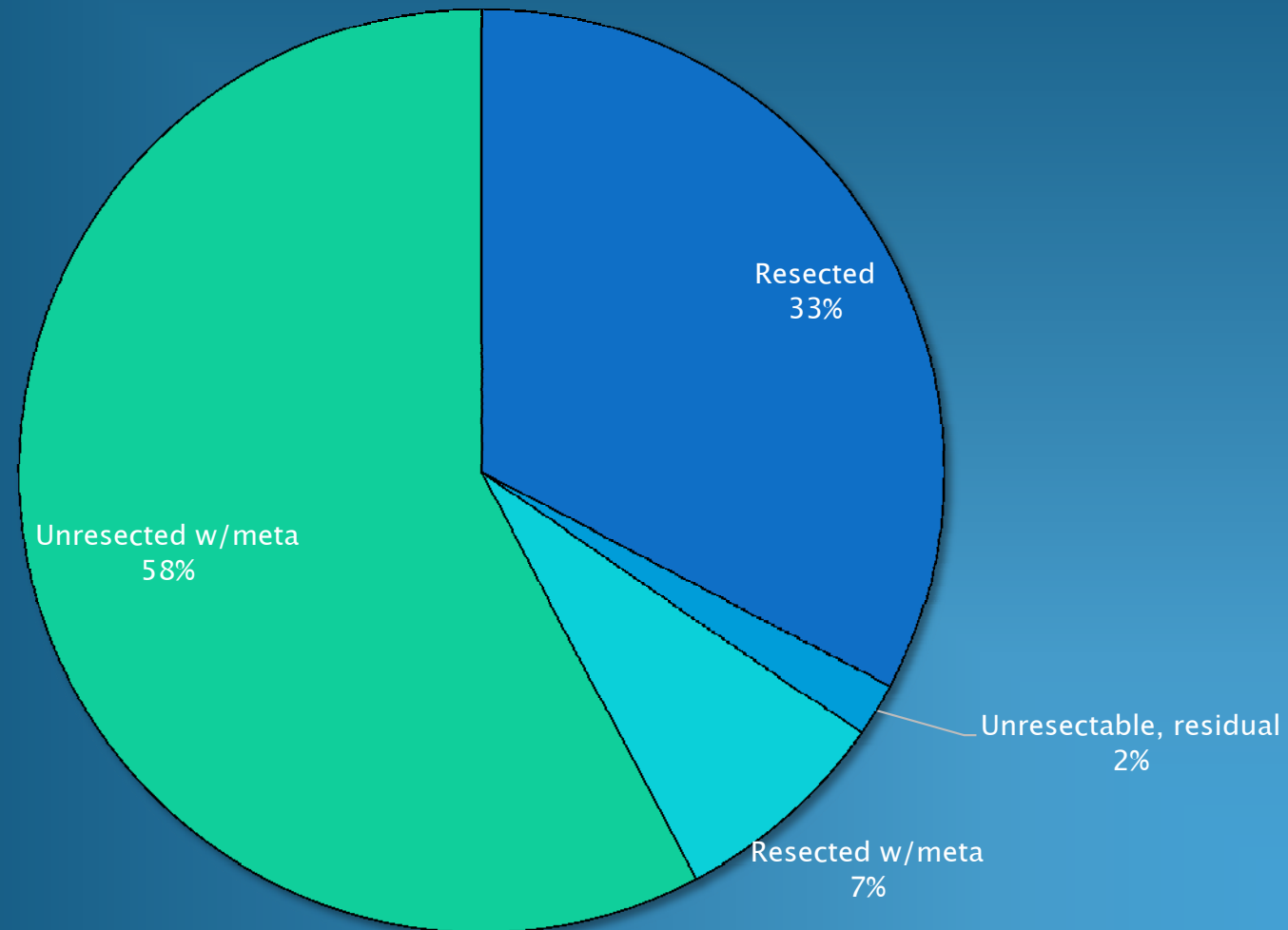
Sample starting oncologic status (cont'd)

Sample distribution by Stage



Sample starting oncologic status (cont'd)

Sample distribution by surgery/metastatic status



Short term effects

Status at end of MT	Total	Colon	Rectal
Progression	2	1	1
No change	11	5	6
Regression	13	6	7

Sample: 26/52

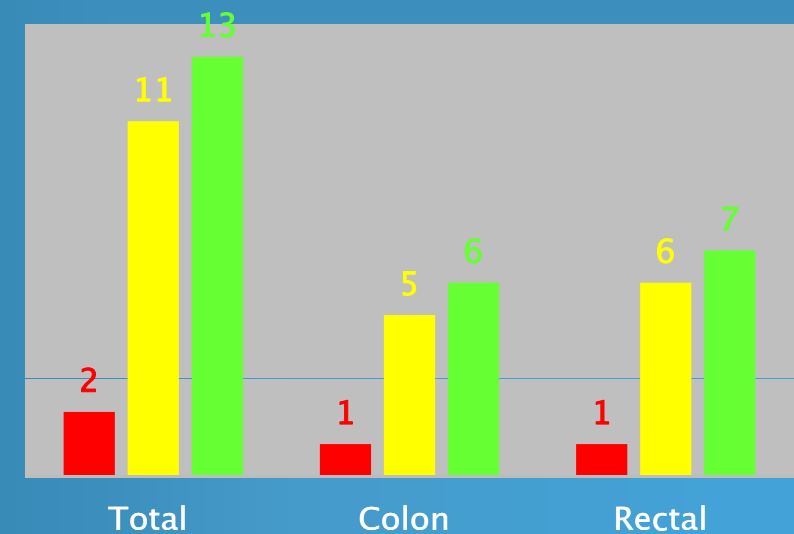
- These effects have been assessed at the end of primary MT (official medical documents)

The use of MT is not coinciding with standard diagnostic procedure and timing, so less data is available;

We can however better distinguish the effects of MT and ST since they are related less strongly

Short term effects distribution

■ Progression ■ No change ■ Regression



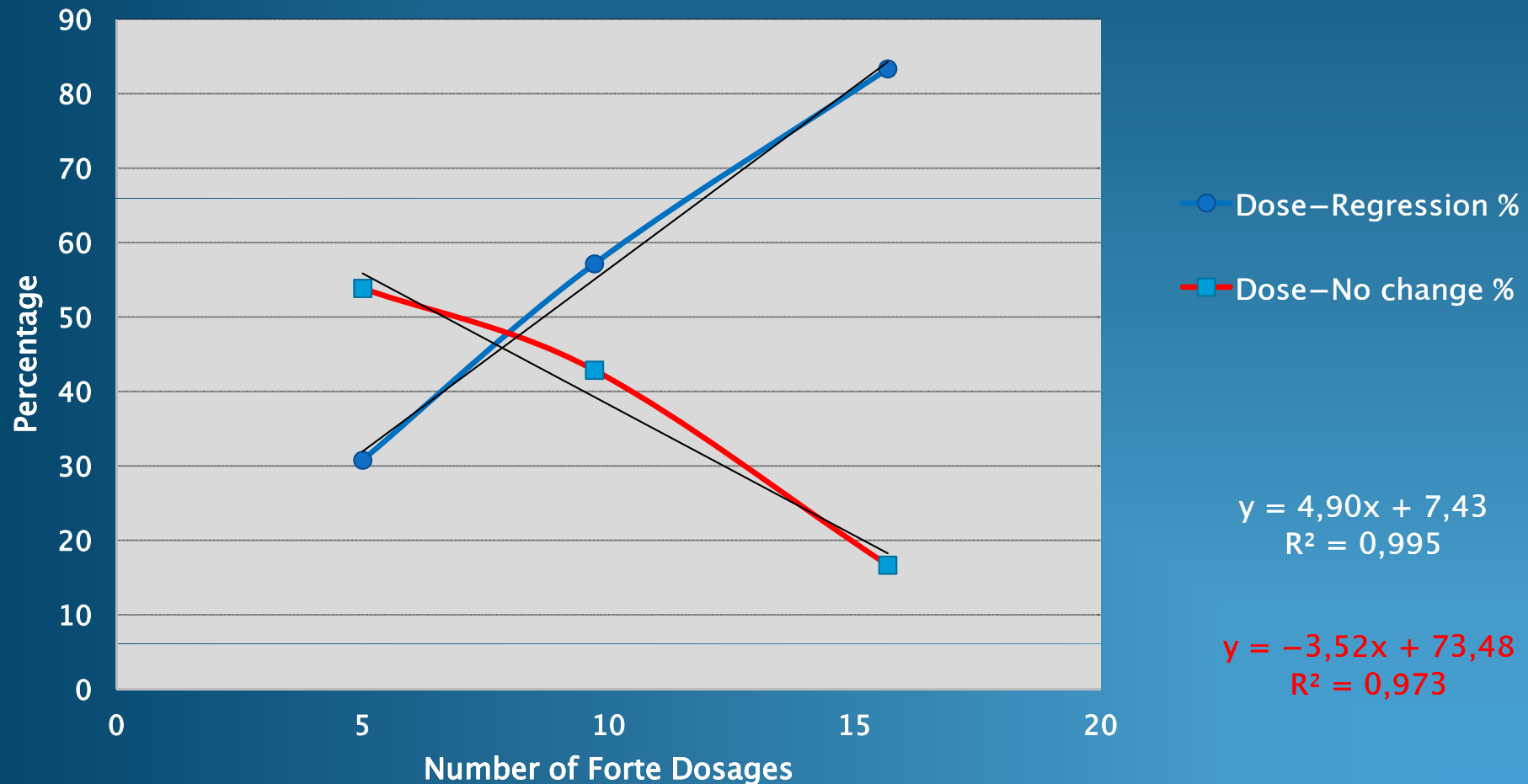
Short term effects (cont'd)

Official therapy procedure is independent of, so we can assess the effects of MT less related to ST

- Patients took 4–27 10–day forte dosages - on average = 7
- Though rate of progression of disease is expected to rise with increased time interval, the patients taking MT preparations for longer time have an increased probability of regression
- Compared to regression rates of the patients on standard chemotherapy 11.7 SD away from the mean!, $p < 0.0005$, sample size 26)

Short term effects (cont'd)

Effects of dosage on regression and no-change rates



The dosages were grouped so each subsample had more than 5 users. This enabled an excellent curve fit.

Effects on metastases (medium term)

- The metastatic status was collected in August 2007 (medium term)

Most commonly metastases target the liver and are inoperable

- Once metastases have developed rates of survival are greatly decreased; **reduction of nonresectable metastases is a major goal** of chemotherapy (with success rates of up to 16%)¹, but it results in vascular changes (blue liver syndrome) and steatohepatitis²

1 Bismuth H, Adam R. Reduction of nonresectable liver metastasis from colorectal cancer after oxaliplatin chemotherapy. *Semin Oncol.* 1998 Apr;25(2 Suppl 5):40–6, PMID: 9609107

2 A. J. Bilchik, G. Poston, S. A. Curley, S. Strasberg, L. Saltz, R. Adam, B. Nordlinger, P. Rougier, L. S. Rosen Neoadjuvant Chemotherapy for Metastatic Colon Cancer: A Cautionary Note. *Journal of Clinical Oncology*, Vol 23, No 36 (December 20), 2005: pp. 9073–9078, DOI: 10.1200/JCO.2005.03.2334

Effects on metastases (cont'd)

- **Meta sample size: 27** (10 alive at end of study)
Metastatic reduction was found in $20.0 \pm 7.6\%$ of sample with no hepatotoxicity

Dosage–effect relationship

- In metastatic disease (/w unresected tumor), increases in a number of dosages shows some effect of meta suppression (slope -0.81 , $R^2=0.68$)
- This result is not statistically significant – sample size is too small to make confident statements of dose dependent results

Long term survival

- All survival rates are given in absolutes, and not relative to age-adjusted general population

Due to small sample sizes we are only able to analyze total survival and survival in stages 3 and 4

- American general 5-year survival rates are much better than rates in Europe (62 vs.43%)¹
- 5-year survival (only US data available)
Stage 3 (US data², A-83%, B-64%, C-44%)
Stage 4 (US data^{3,2}, 5-8 %)
- Median survival (all stages) with ST (standard therapy): 29.2⁴ months after 1st diagnosis

1 European Journal of Cancer

2 According to American Cancer Society; no data for Croatia

3 Data from National Cancer Institute

4 US data 2004-6, large jump from 19 months in 2003

Long term survival (cont'd)

Survival is significantly increased in colorectal cancer patients using mycotherapy

- Median survival in MT sample: **38 months**, avg. 34.06 (with 96.8% confidence that this result is **independent of ST**; outside of confidence interval)
- Additionally, the MT sample has a significant skew to the more difficult cases and was calculated from the **start of MT** and not with first diagnosis!

Survival by stage

Cumulative deaths vs. time

Time (mths)	0–12	12–24	24–36	36–48	48–60	60+	Sample size
Total	15	22	26	33	33	33	51 ¹
Colon	9	12	14	16	16	16	28
Rectal	6	10	12	17	17	17	24

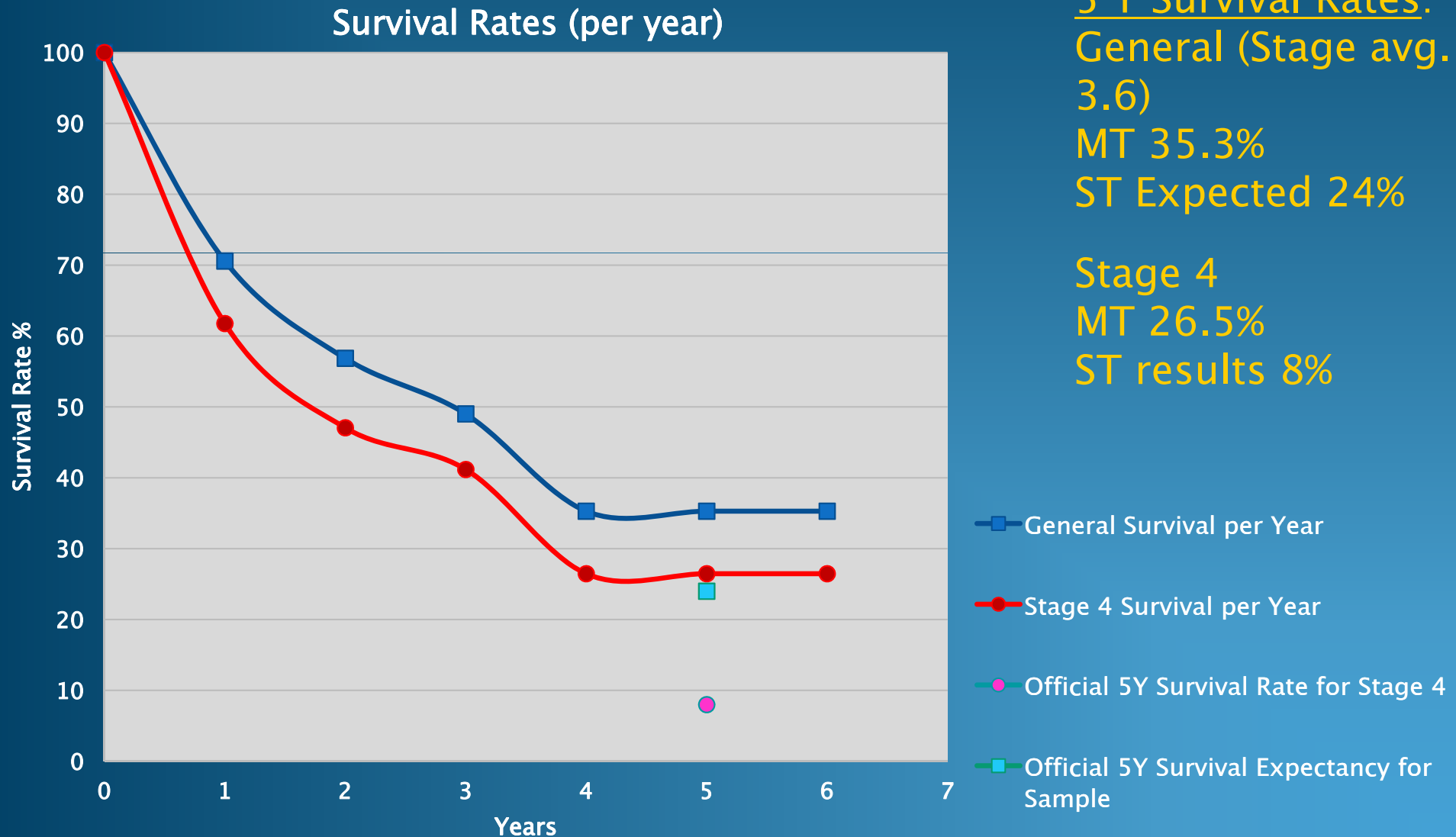
Changes vs. time (dark red=deaths) by TNM Stage

Time (mths)	0–12	12–24	24–36	36–48 ²	48–60	60+	Sample size
1	–	–	–	–	<u>1</u>	–	1
2	–	–	–	–	–	<u>2</u>	2
3	2	2	2	1	<u>2</u>	<u>4</u>	13
4	13	5	2	5	<u>4</u>	<u>5</u>	34

1 Survivors: 18/51 (for 1 person in the sample survival could not be precisely established)

2 1 death in 36–48 months interval is of unknown TNM Stage

Survival % per year



Stage 3 and Survival

- From Stage 3, patients with stages B and C were evaluated (5, 7 in sample, respectively)
- Averaged weighted sum of **USA data** on survival for this group gives expected 5–Y survival of **52.3%**
- The survival in this group was 7/12 (**58.3%**), but the result is not sufficiently significant ($p \approx 0.01$)
- This study also only **measured time from start of MT**, not from the first diagnosis! This will significantly increase the value of this result.
- A larger sample than followed in this study has to be used to find any statistical significance

Stage 4 and Survival

- In our sample, 34 patients were starting in Stage 4
- Official 5–Y Survival from 1st diagnosis is 5–8% (which for this sample amounts to 1.7–2.7/34 survivors)
- In our sample, 9/34 have survived >5 years (26.47%)
- The result is statistically significant:
($P(\bar{x}=0.2647|H_0\text{true})=0.07\%$, $p<0.001$)
- 5–Y survival was measured from the start of MT, compared with the highest official data for 5–y survival from the 1st diagnosis (8%), 98.4% confident that the survival in sample is increased by using MT in Stage 4 cases

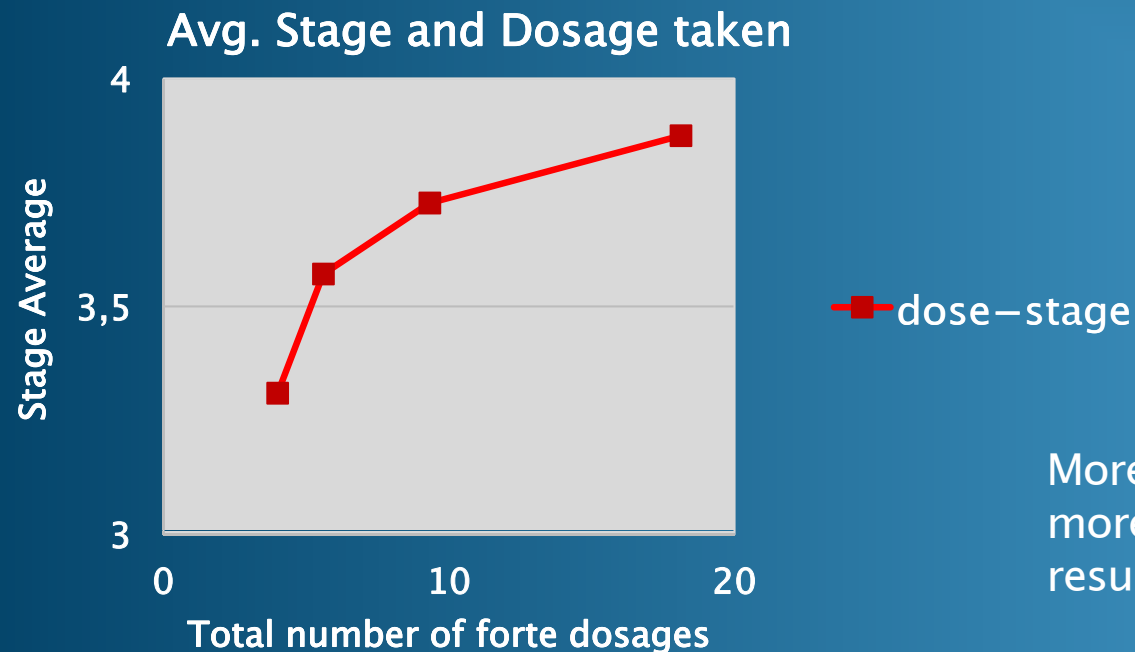
This shows that 5–year survival is significantly increased in colorectal cancer patients using mycotherapy

Dosage-Survival Correlation

Dosage-Effect

Increased dosage, i.e. total number of forte dosages, is positively correlated with longer survival

- This trend appears smaller because of the positive correlation between an dosage increase and more difficult cases



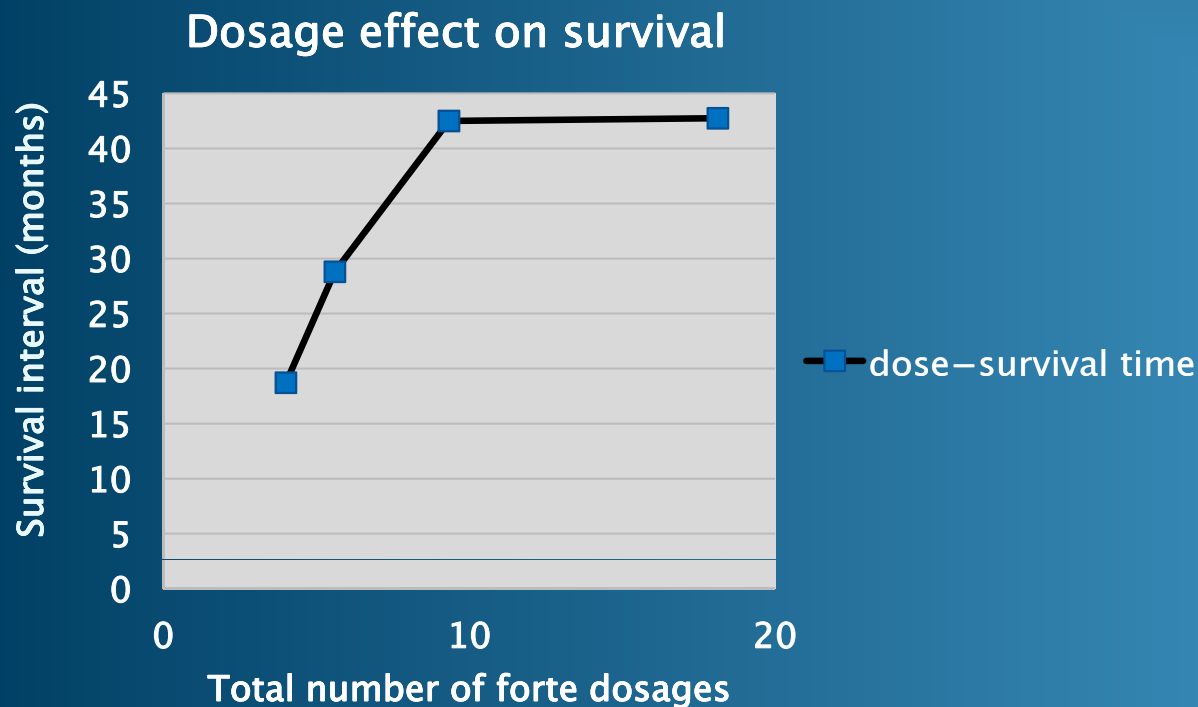
More difficult cases used significantly more forte dosages; this skews the results lowering the perceived benefit

Dosage-Survival Correlation

Dosage-Effect

Increased dosage, i.e. total number of forte dosages, is positively correlated with longer survival

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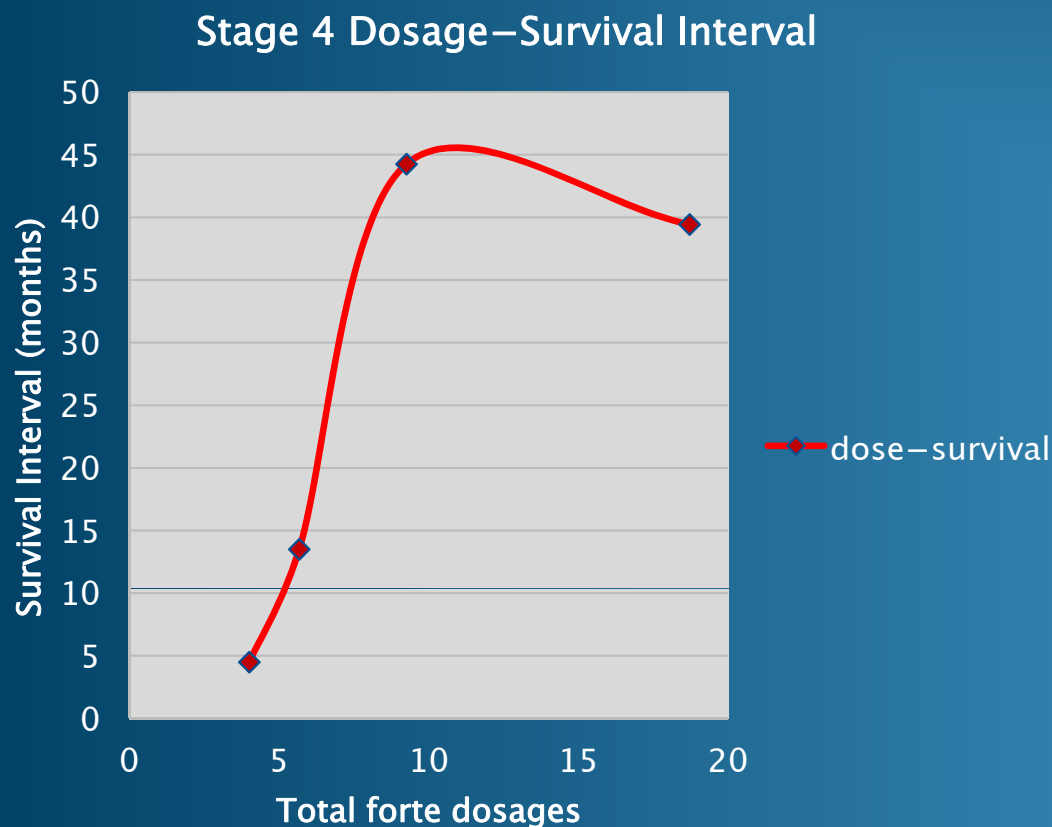


When evaluated up to 10 forte dosages, the correlation is very strong ($R^2=0.98$)

Above 10 forte dosages, there seems to be a threshold or a certain number of people simply do not benefit from increased MT; unfortunately the sample is not big enough to establish it (8 patients took 11–27 dosages, stages 3&4)

Dosage and survival in Stage 4

- In Stage 4, dosage and survival were additionally assessed (separately from other stages)



There is a **very strong correlation** of increased dosage leading to increased survival interval for up to 10 forte dosages

In our sample, more than 11+ dosages did not lead to improvements

This **sample size was just 7** so other possibilities exist – there may be a certain percentage of **non-responders**, irrelevant of the dose

However, there was significant short term improvement in this particular group

A possible negative effect of increasing to 11+ dosages was evaluated with a student t–test, but no statistically significant influence was found ($p > 0.2$)

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Breast Cancer

- Breast cancer is the most common type of cancer in women
- Effect of **chemotherapy is even less powerful** than in colorectal cancer (generally improves survival by just 1.5%)
- Primary treatment method is surgery, which may give a disease-free status and up to 98% 5-year survival rate in certain cases
- Statistics for this cancer type are continually improving; however, the is mostly caused by stage at presentation (earlier diagnosis)

Sample size: 89

Oncological status at the start of MT

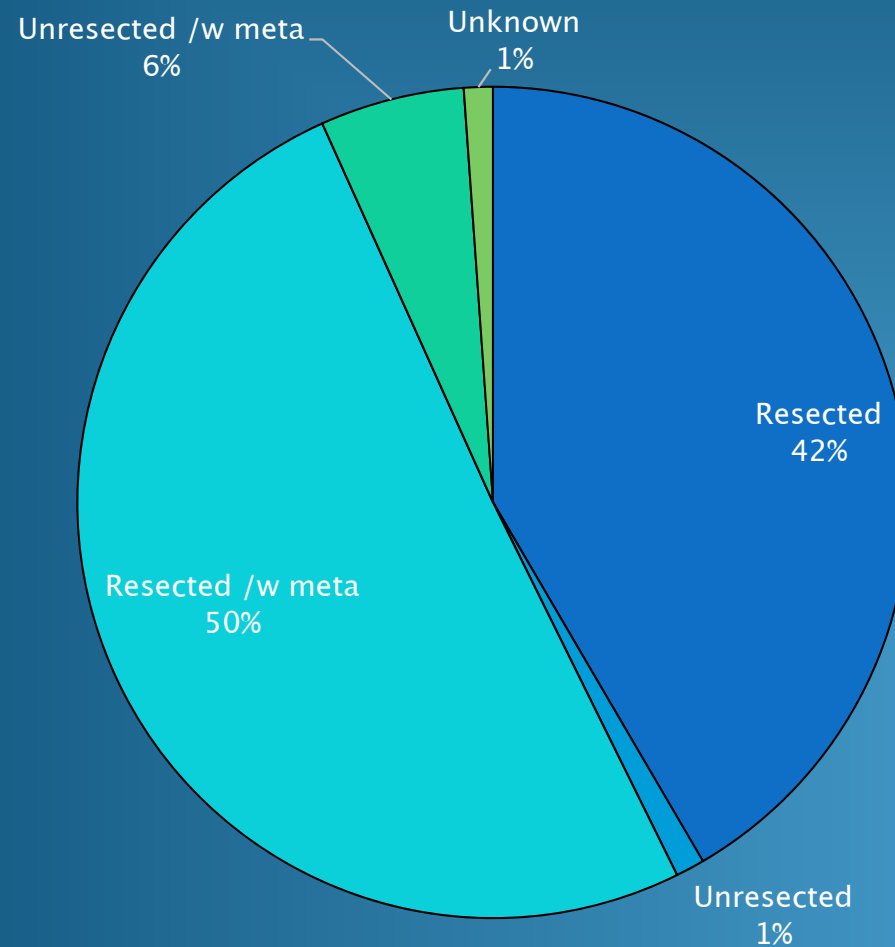
- This sample contains a **disproportional number of metastatic cancer**, skewing the distribution to more difficult cases

Treatment of metastatic breast cancer is primarily palliative, with extremely low rates of improvement (1.5%)

Status	Number in sample
Resected	37
Unresected	1
Resected /w meta	45
Unresected /w meta	5
Unknown	1

Oncological status at the start of MT (cont'd)

Sample distribution of surgery/meta status



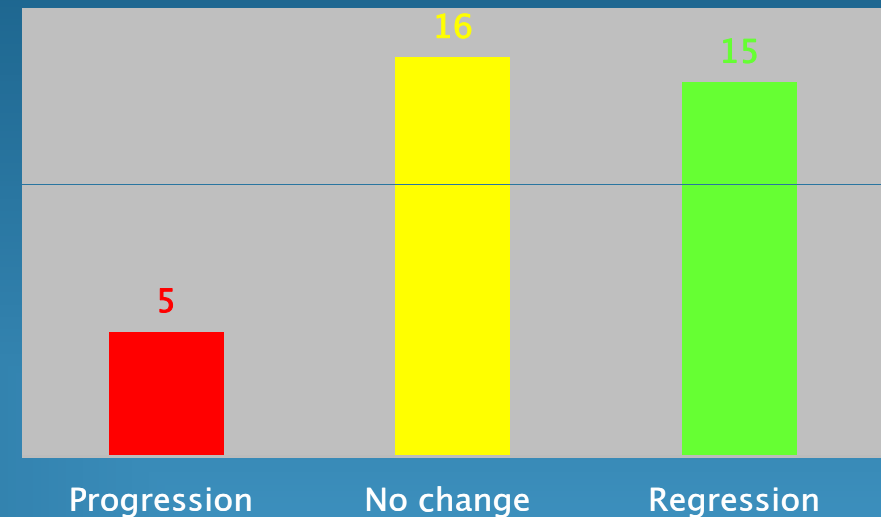
Short term effects

Short term effect	Number in sample
Progression	5
No change	16
Regression	15

Sample size: 36/89

- These effects have been assessed at the end of primary MT (official medical documents)

Short term effects distribution



The probability of such regression rates (41.67% of cases) not being caused by MT (when compared with ST rate of 1.5%) is 19 SD away from the mean; literally of the charts, $p < < 0.0001$; Null hypothesis of no effect on regression beyond ST must be rejected

Short term effects (cont'd)

Dosage–effect

Analyzing the complete known sample, there is both some **increase in regression** as dosage is increased and a weaker, statistically non–significant **increase in progression** of disease

- This reveals an important problem – the influence of various stages of the disease

We tried looking more specifically:

Resected (10) *very small dosage variation*, small dosages (avg. 4.5), 90% no change

Unresected with meta (3), large dosages (avg. 10.67), more progression, *very small sample*

Short term effects (cont'd)

Resected with meta (22), good sample for further analysis

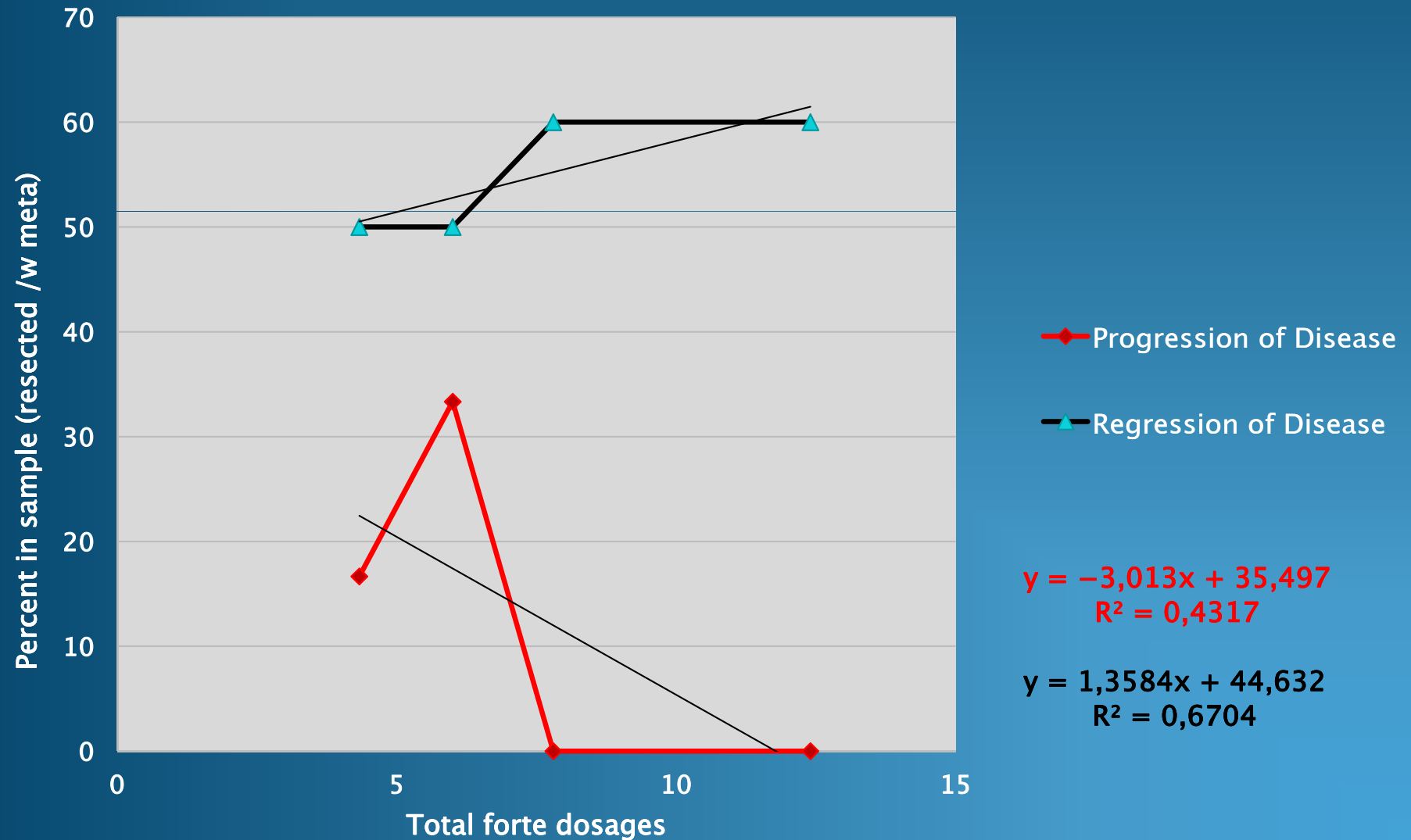
Analysis of this subsample shows a stronger correlation:
*increase in dosage increases regression rates and
lowers progression rates*

- however, neither of these are confident enough to be used to accurately predicting future outcomes, by this model

The results are shown in the following graph...

Short term results

Progression and regression rates vs. dosage



Metastases (medium term) effects

- Assessed at **August 2007** (medium term)

Metastases most commonly target bones, lungs, liver, lymph nodes, and brain

Statistics for this cancer type are continually improving; however, the most important predictor of mortality variation is caused by stage at presentation (earlier diagnosis)¹

- Metastatic breast cancer 5–Y Survival is low (**14 %**)²
- Metastatic breast cancer is usually considered separately from other stages of breast cancer

1 P. Tai, E. Yu, V. Vinh–Hung, G. Cserni, G. Vlastos. Survival of patients with metastatic breast cancer: twenty–year data from two SEER registries.; BMC Cancer, v4.; 2004, doi: [10.1186/1471–2407–4–60](https://doi.org/10.1186/1471-2407-4-60)

2 M.E. Lippman. Breast Cancer, Harrison’s Principles of Internal Medicine, p.516–523; D. L. Kasper et al., eds, 16th ed, 2005

Metastases (medium term) effects

Sample status: 50 (21 alive at end of study)

Metastatic reduction was found in $20.0 \pm 5.7\%$ of MT sample.

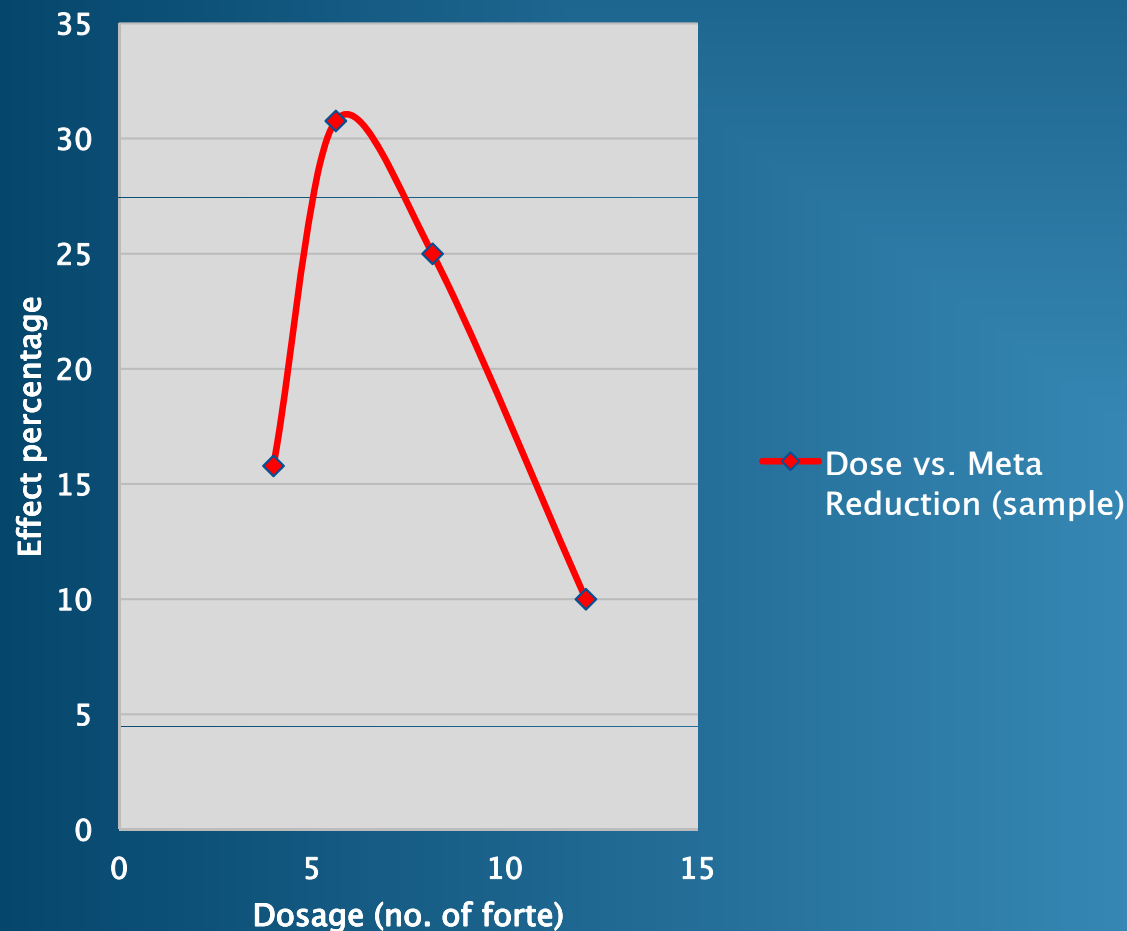
- Metastatic breast cancer is treated with palliative chemotherapy – reduction effects on metastases (1–3%).
- This result is statistically significant ($p < 0.001$)

Dosage–effect relationship

- Increases in dose show seemingly random variations – there may be a problem with a lack of a more stable prognostic factor
- No definite, statistically significant **dose–effectiveness** relationship found

Non-significant meta results

Effects of dosage on reduction of metastases



Dose-reduction of metastases effects cannot be established with appropriate confidence

No statistically significant effects can be deduced (max. between 6–8 forte)

Long term survival

All survival rates are given in absolutes, and not relative to age-adjusted general population

- General 5-year survival rate during the study was at 85%¹; this is time from first diagnosis and with normal population distribution of disease stages (dependent on year and location)
- 5-year survival rate for Stage 4 is 14%² in population from 1st diagnosis
- Croatian official results are not available and are likely worse than the US data quoted above

1 "World Cancer Report". International Agency for Research on Cancer. 2008

2 Marc E. Lippman, *Breast Cancer*, HARRISON'S PRINCIPLES OF INTERNAL MEDICINE, p. 516–523 (D. L. Kasper et al., eds, 16th ed 2005)

Survival results in BrCa sample

Cumulative deaths in sample; total and metastatic

Time (mths)	0–12	12–24	24–36	36–48	48–60	60+	Sample size
Total	28	39	41	49	49	49	89
Metastatic	24	34	35	40	40	40	50
No meta	4	5	6	9	9	9	38

Survivors: 40/89

In 1 case unknown if distant metastases are present

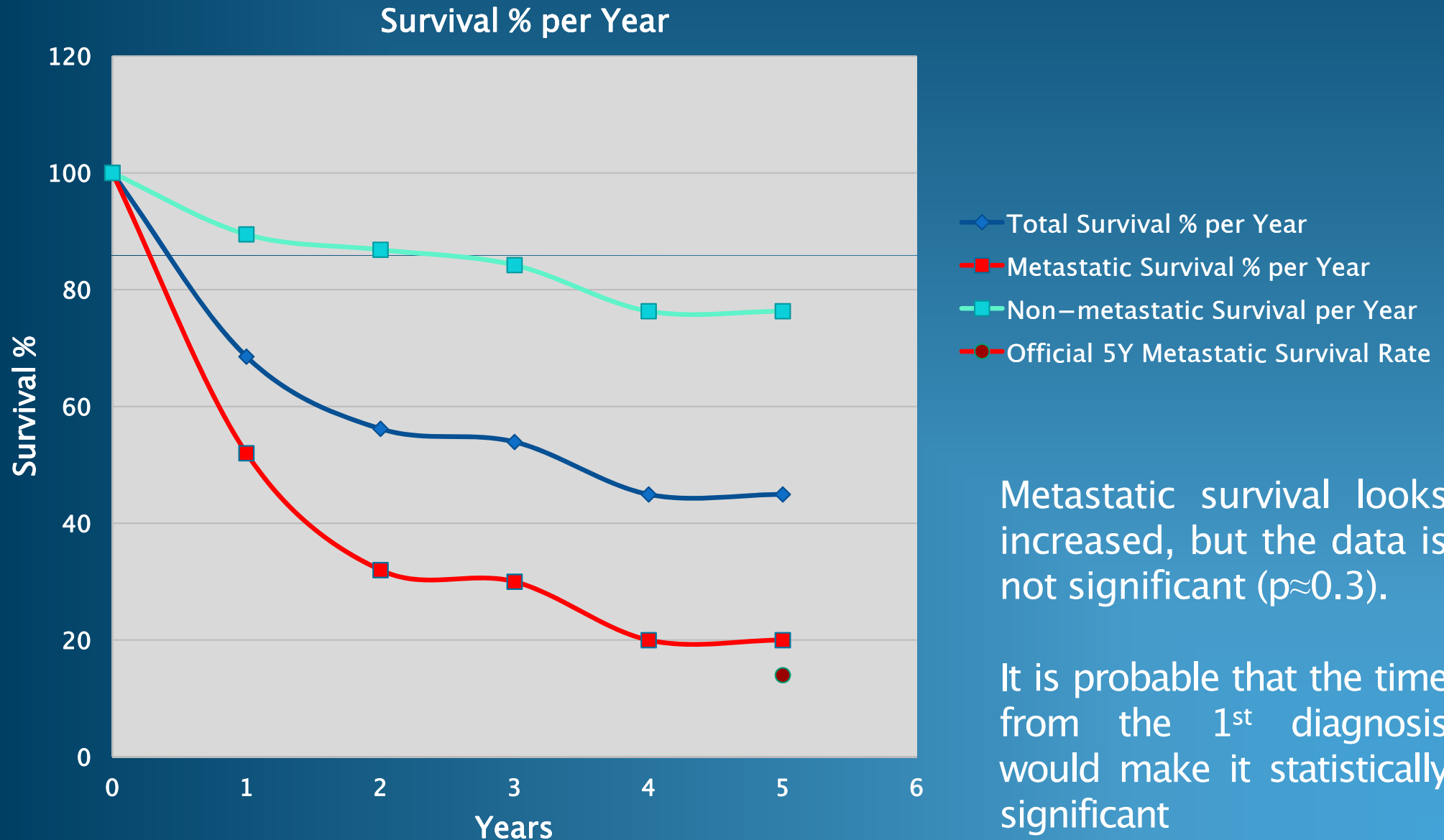
In MT sample: general 5–Y survival was just 44.94%
(sample more difficult than normally distributed in population, but due to insufficient staging data, **we cannot compare it**)

Non–metastatic breast cancer 5–Y survival rate was 76.32% (unknown distribution of stages, **not comparable**)

Metastatic breast cancer 5–Y survival was 20% (vs. 14 in population)

We have insufficient data to compare the effect of MT use on long term survival in total and non–metastatic cancer

Survival % per year

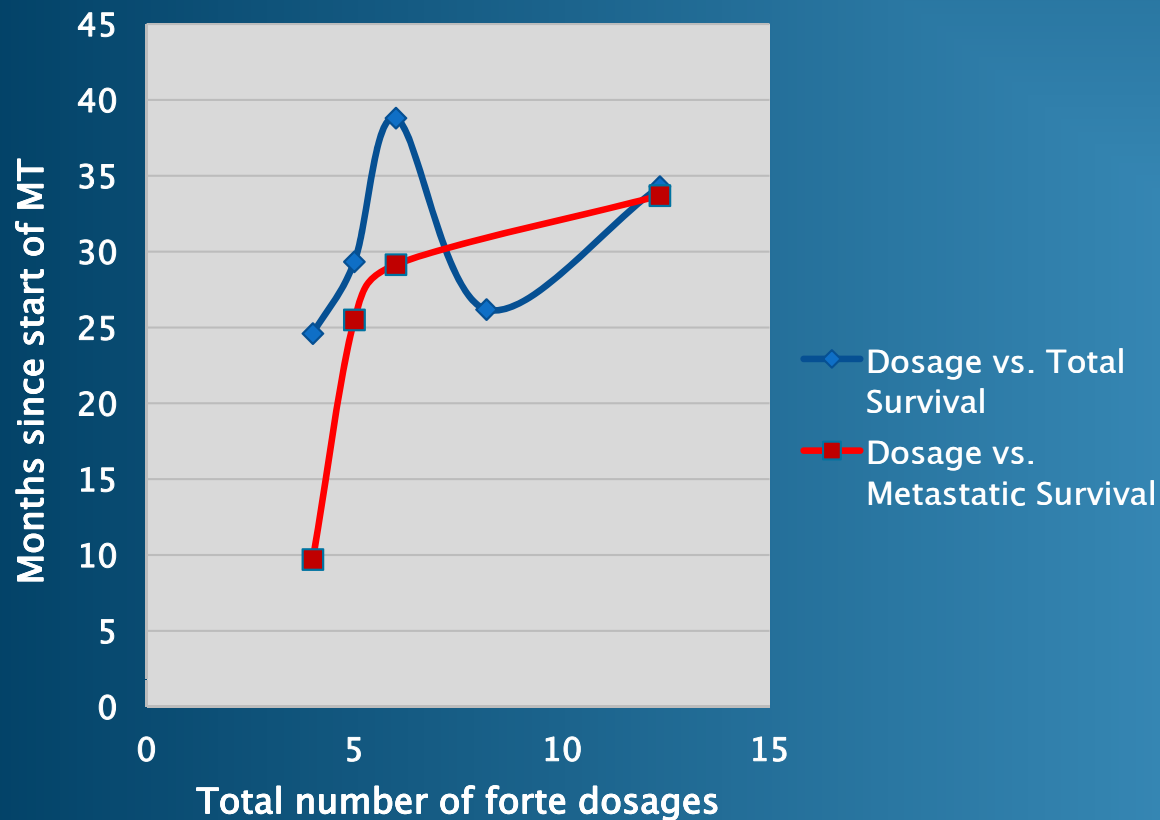


Dosage-Survival Relationship

Increased dosage and increased survival are positively correlated

The results are skewed because more serious cases took larger dosages

Dosage–Survival Interval Relationship



The dosage–survival interval correlation is strongest at the low end (4–6 dosages; 64 patients) of usage ($R^2=0.885$) This suggests a powerful **effect of starting MT**

This skew, caused by increased dosages in more difficult cases (in 7+ dosages just 3/25 cases are non–metastatic), is a **major cause of the dip in the graph from 6–8 forte dosages**

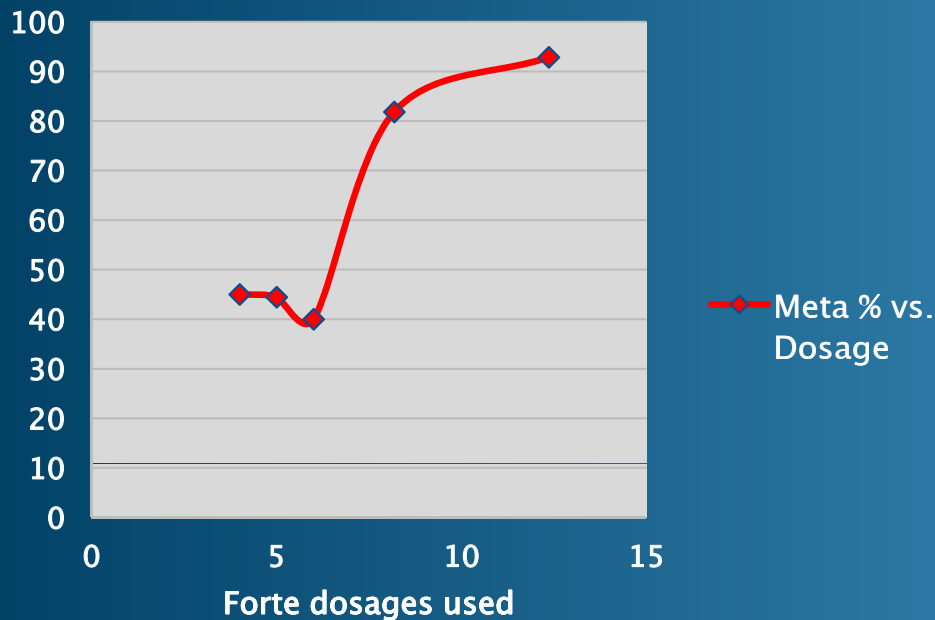
Dosage-Survival Relationship (cont'd)

Increased dosage and increased survival are positively correlated

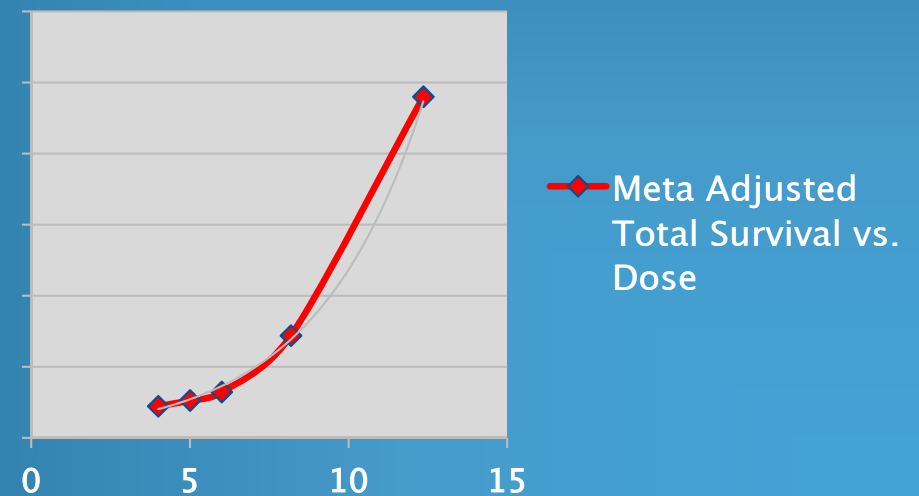
The results are skewed because more serious cases took larger dosages

There is a large increase in the ratio of metastatic cancers between 6–8 dosages!

Meta % vs. Dosage



Adjusting for the skew (proportions of meta) we find a strong dose-dependent effect, and the function is monotonically increasing



This graph shows % of metastatic breast cancer in sample vs. MT usage

The Big Picture: Overview of results

- With larger dosages (=longer use) the rates of cancer regressions rise and rates of progression and no-change in status fall
- The regression effects are dose-dependent, more strongly so in colorectal cancer
- Metastases reduction is strong in breast cancer, while less intense in colorectal cancer
- Dosage-effect relationship is stronger in colorectal cancer, and weaker in breast cancer
- Survival prolongation is strong in colorectal cancer, likely in breast cancer (but cannot be confidently established)
- Dosage-effect on survival is stronger in colorectal cancer, but probable in both
- Starting MT yields fastest results (there is a point of diminishing returns; here established at above 100 days use in both cancers)
- Larger dosage and longer use is safe (no decrease in survival and status)

The bottom line

Did we cure cancer? Did we win?

No.

Mycotherapy results

Colorectal cancer

Short term regression: 50% of cases

Meta reduction: 20%

Stage 4 5Y–survival: 26.5%

Breast cancer

Short term regression: 41.7%

Meta reduction: 20%

Stage 4 5Y–survival: 20%

Standard therapy results

Colorectal cancer

Short term regression: 4% of cases

Meta reduction: 16 % /w side effects

Stage 4 5Y–survival: 8%

Breast cancer

Short term regression: 1.5%

Meta reduction: 1–3%

Stage 4 5Y–survival: 14%

But the results are greatly improved by introducing mushroom therapy.

Thank you for your attention!

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Lessons for the future

For the researchers

The lack of time from 1st diagnosis made a lot of statistics less definite. While it made the actual probabilities more likely than calculated here, we lose some of the comparability value.

The breast cancer needs to be staged better (this was partly the fault of the non-affiliated MDs).

The quantities of the preparation used was dependent on the patient's status, their response to therapy and factors beyond the medicinal. For best results, dosages should be independent of factors disconnected from the trial.

The data collection was very dependent on patient's participation and the thoroughness of their medical personnel.

The lack of information made it necessary to create smaller subsamples. While care was taken that they remain representable of the population, this made certain statistics less confident. The initial sample, should, resources permitting, be even larger than used here, to circumvent this difficulty.

Most of this would be resolved naturally in a full clinical trial.

For the patients

Medicinal mushroom preparations are effective, to a certain degree.

However, there are significant individual variations, which we cannot, at our present state of knowledge, confidently predict.

The very first month or two of use may be crucial in improving short term survival, metastases reduction and total survival increase. Shorter duration is not likely to produce a significant effect.

This could not be determined by the strength of the tests in this study and may not be factual, but MT of 100 days seems ideal. After this period, there is some statistical indication that there is diminished return for the investment. (while not detrimental, there was no significant change in users taking more)

For the medical personnel

The use of mycotherapy (use of medicinal mushroom preparations) in oncological diseases is not harmful, and may be beneficial if used in proper doses (in this study 0.1 g/kg BW per day) for 40–100 days or longer.

The use of higher doses for a longer period is safe. There is a potential point of diminished return in MT lasting longer than 100 days.

The use of MT in colorectal cancer and breast cancer improved regression rates and slowed progression of the disease. The response is highly dose-dependent.

The use of MT had a strong effect in reducing metastases. This result is especially interesting in colorectal cancer, as the effect is without serious side effects often observed in chemotherapy treatments.

Use of proper MT significantly improves 5Y survival rates for colorectal and breast cancer.