

# Brain Metastases in The Netherlands: Results of a Patterns of Care Study

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## ABSTRACT

**Purpose:** Estimation of the incidence of brain metastases, and patterns of care for patients with brain metastases in The Netherlands.

**Methods:** Radiation-oncologists, neuro-oncologists and neurosurgeons, all members of the Dutch Association of Neuro-Oncology (LWNO) were approached to complete a web-based questionnaire. The first part of the questionnaire contained questions about the incidence of brain metastases, the second part was designed to investigate treatment in 8 different imaginary patient cases.

**Results:** Ten radiation-oncologists, eleven neuro-oncologists and five neurosurgeons from 15 hospitals completed the questionnaire (response: 33% - 48%). Five radiation-oncologists could provide incidence information from a patient data registration. Extrapolation resulted in a rough estimate of 3,000 new cases per year referred for radiation therapy (18 per 10<sup>5</sup> citizens); 22% to 29% with a single metastasis. Adherence to the national guidelines for treatment of brain metastases is poor; in only 3 of 13 case descriptions there was more than 70% agreement in treatment policy. Finally, there was little agreement about the necessity and study-questions for future studies on the role of radiotherapy.

**Conclusion:** The number of patients with brain metastases and their treatment in The Netherlands is poorly registered. Hence it is not possible to give a reliable estimate of the incidence other than that the 'number of patients run into thousands per year'. There are major local differences in treatment policies, and only a minority of Dutch brain tumor specialists follows the official Dutch national guideline for brain metastases.

## INTRODUCTION

Brain metastases are common in the course of cancer and usually fatal. In the Netherlands, patients with brain metastases are poorly registered. Therefore, there are no reliable figures on the number of patients with brain metastases, whether they have single or multiple brain metastases, or what the

outcome of treatment is. However a better understanding of the nature and the number of patients with brain metastases is needed to provide better health care for these patients, and to identify priorities for scientific studies. It has already been established that the number of patients is high, that the morbidity is severe

and that the survival rate with the current treatments is still very poor.

Foreign population studies estimated the incidence of patients with brain metastases at around 10 per 100,000 people.<sup>1,2</sup> For the Netherlands this would come down to 1,700 patients with brain metastases annually. Based on clinical studies and autopsy studies, the incidence could possibly be much higher.<sup>1,2</sup> Moreover, the results of primary cancer treatment are improving, so that more patients live long enough to develop brain metastases.

A revision of the Dutch national guideline for brain metastases was published in 2011. This guideline advises certain treatment policies based on prognostic factors.<sup>3</sup> Since then, a number of randomized trials has been published that may cast doubt on specific treatment recommendations in the guideline.  
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Radiotherapy and surgery, in addition to Best Supportive Care (BSC) with corticosteroids, are the most commonly used treatments for patients with brain metastases. In radiotherapy, there are three commonly used techniques: Stereotactic radiosurgery (SRS), fractionated stereotactic radiotherapy (FSRT), and whole brain radiotherapy (WBRT). The choice of treatment depends on the number, size and location of the tumor and the extent of extracranial disease. The most important prognostic factors for brain metastasis survival are general condition, age, control of the primary tumor, presence of extracranial metastases, number of brain metastases and response to corticosteroids.<sup>9,10</sup> The median survival is 3 to 4 months; the median survival in the most favorable group after resection, is 9 to 10 months. These poor results of treatment of brain metastases show us that we urgently need more research and clinical trials.

## PURPOSE

We conducted a Patterns of Care study to investigate the feasibility of a national study in patients with brain metastases. Therefore we wished to estimate the number of patients with single and multiple brain metastases. A second objective was to gain insight into the current treatment practice.

## METHODS

A Patterns of Care study was conducted among neurosurgeons, neuro-oncologists and radiation-oncologists whom were connected to the Dutch Association for Neuro-Oncology (LWNO). An online survey was conducted with SurveyMonkey™ and was sent to all LWNO members, with a reminder email after four weeks. The Patterns of Care survey consisted of two parts.

The first part was different for each specialism (10-14 questions). It contained questions to estimate the size of each center in beds per unit and number of patients treated per year and the number of patients treated for brain metastases in 2012. We next asked how many of these patients had a single brain metastasis.

To gain insight into the validity of the answers, we asked how the respondents came to their answers ('formally registered patients', 'best guess', 'otherwise, i.e.'). Furthermore, we asked the specialists how many patients were referred to another specialists. For the radiation-oncologists we added six additional subject-specific questions regarding radiotherapy techniques.

The second part of the survey contained eight imaginary patient case descriptions (13 questions). The specialists were asked to choose a policy, and if desired, to explain their choice. Furthermore, we asked the specialists their judgment on the purpose and usefulness of adjuvant radiotherapy after resection of a single brain metastasis (2 questions).

## RESULTS

A total of 26 specialists completed the questionnaire. There were 10 radiation oncologists, 11 neuro-oncologists and 5 neurosurgeons, coming from 15 clinics. For both the radiation-oncologists and neurosurgeons this means a coverage of 48%-50% of the neuro-oncological care in The Netherlands.

Table 1 gives an overview of the participants, with the number of patients they treated with brain metastases in 2012, and the clinic sizes.

**Table 1.** Summary of participating specialists estimate of number of patients with brain metastases and the size of the department of new patients per year.

	Radiation-oncologists		Neuro-oncologists		Neurosurgeons	
	patients with brain metastases	clinic-size	patients with brain metastases	clinic-size	patients with brain metastases	clinic-size
	325	5000	50	1500	45	500
	75	4000	80	1400	30	450
	150	4000	20	1200	30	400
	190	2800	1 20	1100	30	200
	100	2100	40	110	30	150
	99	1500	150	n.s.		
	55	1350	125	n.s.		
	30	700				
	250	600				
<i>Total</i>	12 74	22,050	585	5,310	165	1700
<i>Average per clinic</i>	141.6	2,450.0	83.6	1,062.0	33. 0	340.0

*n.s. = not specified*

#### *Radiation-oncologists*

Ten radiation oncologists specialized in neuro-oncology from all 21 approached radiotherapy departments completed the survey (response rate 48%). Together, they treated a total of 1,274 new patients with brain metastases in 2012: An average of 142 patients per department (see Table 1). 21% (273 patients) had a single brain metastasis. Five radiation-oncologists obtained their figures from a patient registry and five radiation-oncologists based the number on a 'best guess'.

#### *Neuro-oncologists*

Ten neurologists from the 25 approached neurology departments completed the survey, three respondents indicated that they couldn't give any reliable numbers of patients with brain metastases, because they were less involved in treating these patients. Together, seven neuro-oncologists estimated that they had treated 585 patients with brain metastases. An estimated 29% (170 patients) had a single brain metastasis. None of the

neurologists kept a formal registration of patients with brain metastases, so all the numbers were based on best guess estimates. Of the 585 patients, 74.5% were referred to a radiation-oncologist, 11% were referred to a neurosurgeon and 14.5% were not or to elsewhere forwarded. An estimated 89 (15%) patients were treated exclusively with best supportive care.

#### *Neurosurgeons*

Five of the 10 approached neurosurgeons (50%) operated a total of 165 patients for brain metastases. 82% (135 patients) had a single brain metastasis. All the neurosurgeons provided best guess estimates.

#### *Estimation of the incidence*

Based on 10 of the 21 approached neuro-oncological radiation-oncologists (48%), there were approximately  $1 / 0.48 * 1,274 = 2,654$  patients irradiated for brain metastases in 2012. Considering that 15% of the patients

are, according to the neurologists, only treated with best supportive care, we can estimate that the incidence of brain metastases is more than 3,000 patients each year. Out of a population of 16.7 million residents in 2012 that comes down to 18 per 100,000 inhabitants. Approximately 25%, about 750 patients, have a single brain metastasis.

### Therapeutic policy

We next attempted to get an impression of the differences in the therapeutic policies and adherence to the Dutch Guideline for Brain Metastases by eight case descriptions. Table 2 summarizes the answers to the different case descriptions. For example, figure 1 gives the distribution of recommended strategies 'by radiation-oncologists after a radical resection of a patient with a single brain metastasis. Three answered that they usually 'don't give adjuvant radiotherapy, two advised FSRT, four advised SRS and one would add WBRT. Among the fractionated schedules, three different dose-fractionation schedules were used, and also within the same departments several different schedules were used.

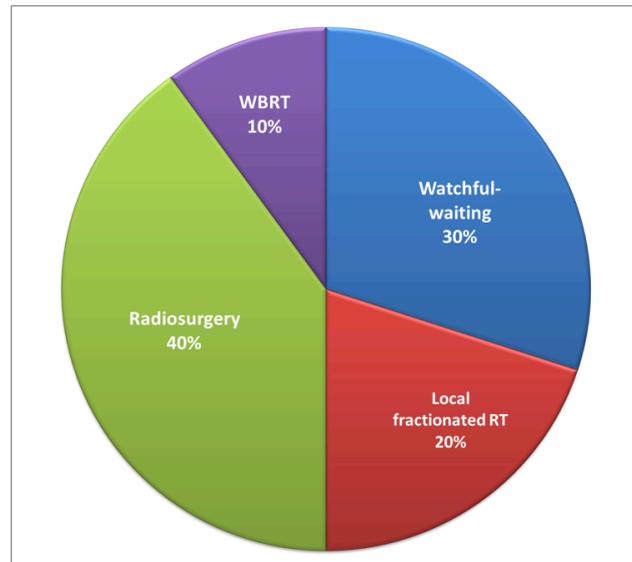
With one exception, all the radiation-oncologists advised adjuvant WBRT after a radical resection of one to three brain metastases. Six respondents recommended 5 fractions of 4 Gy, one respondent advised 2 fractions of 8 Gy and one radiation-oncologist would apply 10 fractions of 3 Gy.

There was more consensus regarding the schedules for SRS for a single brain metastasis. One fraction of 17 Gy to 22 Gy or three fractions of 8 Gy or 8.5 Gy was advised, depending on the size of the tumor.

## DISCUSSION

In this study we found that the adherence to the Dutch Guideline for patients with brain metastases is poor. In only three out of 13 scenario's, the guideline was followed by more than 70% of the respondents.<sup>4</sup> Furthermore, we discovered that, with the exception of some radiotherapy departments, patients with brain metastases are not formally registered. Therefore, the incidence of brain metastases in the Netherlands is largely unknown.

**Figure 1.** Adjuvant radiotherapy after radical resection of a single brain metastasis



Our estimate of 3,000 patients per year, of whom 570 (19%) to 870 (29%) have a single brain metastasis, should be interpreted with great reserves, due to several limitations:

- The incompleteness of response (33% - 50%);
- The large differences among the respondents in the ratio between the size of the clinic (number of admissions per year) and the number of patients with brain metastases in 2012;
- The large variation in the proportion of patients with single brain metastases compared to the total amount of patients with brain metastases, ranging from 5% to 45%;
- The majority of the estimates (83%) is based on 'best guesses'. Only in five cases, all of radiation-oncologists, numbers were based on a data-recording;
- Not all patients are referred to the specialists we have interviewed, some are treated palliatively by other specialists.

In The Netherlands in 2012, 101,373 inhabitants of The Netherlands were diagnosed with cancer (excluding basal cell carcinoma), and 43,139 Dutch persons died from cancer.<sup>11</sup> Provided that our estimate of 3,000 patients with brain metastases is correct, 3% of cancer patients develop clinically relevant brain metastases. These patients usually die within a year and carry a large risk for developing severe morbidity. A uniform treatment of all relevant specialist is

**Table 2.** Treatment preferences on a patient with a single brain metastasis.

Case	Elements case descriptions				Guideline advice	Answers						
	Tumorsize	KPS	Symptoms	Resection		SRS	local FRT	WBRT	Resection	Wait-and-see	BSC	Different
1a	2cm	>70	yes	feasible	SRS or resectie	96%	-	-	0%	-	-	4%
1b	2cm	>70	-	status after radical resection	Wait-and-See	8%	29%	8%	-	54%	-	-
1c	2cm	>70	-	residue after resection	SRS or WBRT	38%	46%	8%	-	-	-	8%
2	2cm	>70	yes	not feasible	SRS	96%	-	-	-	-	-	4%
3a	2cm	50	yes	feasible	Best supportive care	38%	-	8%	4%	-	29%	21%
3b	2cm	50	yes	status after radical resection	Wait-and-See	4%	8%	-	-	83%	-	4%
3c	2cm	50	yes	residue after resectie	Best supportive care	17%	13%	8%	-	-	54%	8%
4	2cm	50	no	feasible	Best supportive care	44%	-	-	-	-	56%	-
Radiologic progression six months post radiosurgery:												
5	-	-	no	feasible	Resection	4%	-	-	26%	17%	-	52%*
6	-	-	yes	not feasible	SRS or WBRT	13%	17%	4%	-	22%	-	44%*
7a			yes	feasible	Resection	-	4%	-	65%	-	-	30%*
7b			yes	residue after resectie	SRS or WBRT	30%	39%	13%	-	4%	-	13%
8			yes	not feasible	SRS or WBRT	22%	26%	8%	-	-	-	44%*

KPS = Karnofsky Performance Score; SRS = Stereotactic Radiosurgery; FRT = Fractionated radiotherapy; WBRT = Whole brain radiotherapy; BSC = Best Supportive Care \*Much cited comment: exclude radionecrosis by perfusion MRI.

needed to improve the morbidity and increase life expectancy.

We compared our inventory of choices of treatments with the revised Dutch National Guideline on Brain Metastases.<sup>3</sup> As this study shows, the guideline is followed by only a narrow majority of neuro-oncology specialists. A possible explanation for the discrepancy is that the guideline is not always based on 'best clinical evidence' for radiotherapy in randomized trials.<sup>5</sup> Noteworthy is that the vast majority recommends, in accordance to the guideline, radiosurgery in 'a patient in a good condition with a solitary brain metastasis, both fit for surgery and radiosurgery'. This is controversial, because a review of randomized trials of Scoccianti et al (2012)<sup>5</sup> suggested that resection gives a greater survival benefit than radiosurgery.

'After radical resection of a solitary brain metastasis' the guideline recommends a wait-and-see policy with a three-monthly follow up by MRI controls. However, nearly half of the respondents ignored the guideline recommendation, and would give adjuvant radiotherapy. The poor adherence to the guideline reflects the conflicting literature. The review by Gaspar et al (2010) suggests that resection followed by radiotherapy (WBRT) improves local control and overall local in the brain, compared with resection alone.<sup>12</sup> The same was found in a recent EORTC study.<sup>4</sup> However, the improvement of tumor control in the brain, did not result in a survival benefit or in improvement of the quality of life.<sup>4,6</sup> Furthermore, there is little evidence that MRI-surveillance improves survival or the quality of life, but they do increase the medical costs and the burden upon patients.

Another difficult controversy, the indication of radiotherapy in patients with more than one brain metastasis, was not investigated in this study.

## CONCLUSIONS

Brain metastases represent a frequent and often fatal complication of cancer. The results of this study suggest that the incidence of brain metastases (~ 3,000 patients per year), is about twice as high as indicated by the Netherlands Cancer Registration. Due to the absence of a formal registration we are even less informed about the treatments and the results of these treatments. There are large regional differences in treatment preferences. Only a minority of the neuro-

oncology specialists follow the Dutch guideline for brain metastases.

## RECOMMENDATIONS

It is recommended to

- improve central registration of patients with brain metastases, their treatment, and outcome.
- base a renewed guideline on best available evidence that results in a greater adherence to the guideline and consequently better treatment results.

## References

1. Fox BD, Cheung VJ, Patel AJ, Suki D, Rao G. *Epidemiology of metastatic brain tumors. Neurosurg Clin N Am.* 2011;22(1): 1-6.
2. Stelzer KJ. *Epidemiology and prognosis of brain metastases. Surg Neurol Int.* 2013;4(Suppl 4):S192-202.
3. Gijtenbeek JM, Ho VK, Heesters MA, Lagerwaard FJ, de Graeff A, Boogerd W. *Richtlijn 'Hersenmetastasen' (revision) [Practice guideline 'Brain metastases' (revision)]. Ned Tijdschr Geneeskd.* 2011;155(52):A4141.
4. Kocher M, Soffiatti R, Abacioglu U, et al. *Adjuvant whole brain radiotherapy versus observation after radiosurgery or surgical resection of 1–3 cerebral metastases: Results of the EORTC 22952–26001 study. J Clin Oncol.* 2011;29:134–41.
5. Scoccianti S, Ricardi U. *Treatment of brain metastases: review of phase III randomized controlled trials. Radiother Oncol.* 2012;102(2):168-79.
6. Soffiatti R, Kocher M, Abacioglu U, et al. *A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. J Clin Oncol.* 2013;31(1): 65-72.
7. Hasan S, Shah AH, Bregy A et al. *The role of whole-brain radiation therapy after stereotactic radiation surgery for brain metastases. Pract Radiat Oncol.* 2014;4:306-315.
8. Soon YY, Tham IW, Lim KH, Koh WY, Lu JJ. *Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases. Cochrane Database Syst Rev* 2014;

- 3 :CD009454. doi: 10.1002/14651858.CD009454.pub2.
9. Gaspar L, Scott C, Rotman M *et al.* Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys.* 1997;37:745–751.
  10. Lagerwaard FJ, Levendag PC, Nowak PJ, Eijkenboom WM, Hanssens PE, Schmitz PI. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *Int J Radiat Oncol Biol Phys.* 1999;43(4):795-803.
  11. Netherlands Cancer Registry - Integraal Kankercentrum Nederland (IKNL). [www.cijfersoverkanker.nl](http://www.cijfersoverkanker.nl) (last visited: November 28<sup>th</sup>, 2014)
  12. Gaspar L, Mehta M, Patchell R, Burri S. The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neuro-Oncol.* 2010;96(1):17-32.