Radiotherapy in bone metastasis : the Dutch bone metastasis study

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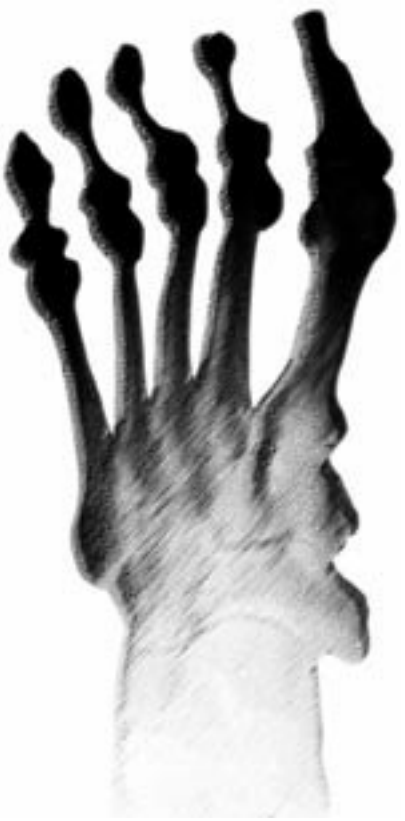

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Discussion and future perspectives

Discussion and future perspectives

In this thesis, the results of the Dutch Bone Metastasis Study on the treatment of painful bone metastases in 1157 patients are presented. The purpose of this trial was to prove the equal effectiveness of two palliative radiotherapy treatment schedules: a single fraction of 8 Gy versus 24 Gy in 6 fractions.

This chapter addresses the implications of the Dutch Bone Metastasis Study as well as bone metastasis related issues that need further investigation.

Methodology Issues in Bone Metastases Research

Major criticism in bone metastases research has been the heterogeneity in design of the published randomized clinical trials with different end point definitions and various patient populations. Therefore, in 2000, an International Bone Metastases Consensus Working Party was initiated in order to promote consistency in endpoint definitions in future clinical trials on the treatment of patients with painful bone metastases. This international effort resulted in a written consensus[1] and an ongoing close cooperation between dedicated researchers. Participants in the consensus filled out surveys containing preferences on bone metastases related issues, and visited the consensus meeting in Boston, USA in October 2000 at the ASTRO Annual Conference.Among others, the consensus stated that retreatment should not be included in the primary outcome of the first irradiation, response to retreatment should be separately analyzed, and changes in analgesics intake should be corrected for in the response calculations.

Some questions regarding bone metastases research are still open for discussion and/or need more research:

Timing of pain response assessment

Response can be measured at fixed time-points (i.e. at 1, 2, and 3 months), as was promoted in the consensus, or as a response occurring at any time during follow up.[1] Criticism to the latter method is that a response occurring beyond 3 months may reflect secondary interventions, such as a retreatment, changes in systemic therapy or adjustments in analgesics intake. Response percentages may then become higher. This method, however, does reflect the response pattern in time, especially when response is shown graphically. In the DBMS, which was designed before the consensus meeting, we chose to use the latter of the two methods. Almost all responses occurred within the first 3 months after randomization. [2] In future, we think reporting response using both methods will give the best information.

Individual pain response

Large differences exist in response patterns between the individual patients.

After palliative treatment, four categories of responders can be pointed out: immediate responders (within a week), intermediate responders (within 4 weeks), slow responders (within 8 weeks), and no responders (personal communication with J.C. van Houwelingen). Even within the same primary tumors, patients may respond differently. More research needs to be done on the course of pain during and after treatment in relation to patient' characteristics.

Effects of co-interventions on pain relief

Another modulating effect on pain other than radiotherapy is the concomitant use of analgesics or systemic treatments. Patients with bone metastases often use analgesics when referred for palliative radiotherapy. Approximately 33% of the patients also have visceral or other metastases and require a more systemic treatment to treat their disease. In the DMBS more than 50% of the patients received some kind of systemic therapy concomitantly. [2] It is obvious that changes in analgesics intake or systemic therapy may infl uence the pain experienced by the patient and can interfere with response calculations. Although the consensus stated that changes in analgesics intake should be corrected for, the precise way in which all treatments interact is unknown. More research on treatment interactions in relation to reported pain needs to be performed.

Quantification of response duration

Although response percentages of 60% to 70% to palliative radiotherapy for bone metastases have been reported, still a large percentage of the patients experiences progressive pain after initial treatment. Most published trials reported progression rates between 28% to 61% of the patients who responded to initial radiotherapy. [3] These patients need a second irradiation or other treatment modalities. Thus, reporting only response percentages does not refl ect optimally the true effect of a palliative treatment. Another method to report the durability of relief is by using the net pain relief (NPR), i.e. the duration of response related to the survival of the patient. [3] The NPR was not frequently used in the literature to evaluate effectiveness of palliative radiotherapy, but we think it is a worthy tool in objectively addressing response duration. At the 2004 annual meeting of the European Society of Therapeutic Radiation and Oncology a study by Foro Arnalot et al was presented on 8 Gy single fraction vs. 30 Gy in 10 fractions. In 160 patients no differences in NPR were observed: 68.5% to SF vs. 71.7% to MF (P= 0.55). [4]

Dose-response relationships in randomized clinical trials on bone metastases

Several prospectively randomized trials focused on the treatment of painful bone metastases with different radiotherapy treatment schedules, ranging from a single fraction (SF) to more protracted regimens *(Table 1)*. Although these studies had different designs and used various kinds of pain scales, some authors have succeeded in pooling the numerous data. In 1999, Ratanatharathorn et al published a systematic review of 12 trials, and concluded that higher dose fractionated treatments produced better pain outcomes than low-dose regimens. [3] They commented that duration of pain relief was much less than the period of survival after treatment. A response analysis on 5 trials by Ben Josef et al was also in favor of multiple fractions. They demonstrated a clear dose-response relationship for pain relief, with higher responses in trials with a biological effective dose (BED) > 14.4 Gy, i.e. above 8 Gy single fraction. [5] In 2002, McQuay on the other hand concluded in his Cochrane Review on 12 trials that there was no evidence of any difference in

TABLE 1 PROSPECTIVELY RANDOMIZED TRIALS OF DIFFERENT RADIOTHERAPY TREATMENT SCHEDULES FOR PATIENTS WITH PAINFUL BONE METASTASES

Trials comparing single fraction versus multiple fraction regimens				
Author/country	**Year**	**Treatment arms**	**Patients R*/ A**	**Analysis reviewed by**
Foro Arnalot (4)	2004	8Gy SF vs, 30Gy /10F	160 / NS	
van der Linden (32), Holland†	2004	-	1171 / 1099	-
Hartsell (12), USA	2003	8Gy SF vs. 30Gy /10F	949 / 897	-
Roos (13), Australia/New Zealand	2003	8Gy SF vs. 20Gy /5F	90 / 79	-
Kirkbride (9), Canada	2000	8Gy SF vs. 20Gy /5F	398 / 278	Wu
Bone Pain Trial Working Party (7), UK/New Zealand	1999	8Gy SF vs. 20Gy /5F	761 / 681	Wu
Steenland (2), Holland	1999	8Gy SF vs. 24Gy /6F	1171 / 1073	Wu
Koswig (33), Germany	1999	8Gy SF vs. 30Gy /10F	107 / 107	Wu
Nielsen (34), Denmark	1998	8Gy SF vs. 20Gy /5F	241 / 207	Wu, Ratanatharathorn, McQuay
Gaze (35), UK	1997	10Gy SF vs. 22.5Gy /5F	265 / 240	Wu, Ratanatharathorn, McQuay
Kagei (36), Japan	1990	SF vs .MF	30 / 27	Ratanatharathorn, McQuay
Cole (37), UK	1989	8Gy SF vs. 24Gy /6F	29 / 29	Wu, Ratanatharathorn, McQuay
Price (38), UK	1986	8Gy SF vs. 30Gy /10F	288 / 97	Wu, Ratanatharathorn, Ben-Jozef, Mc
Trials comparing different multiple fraction regimens				
Author/country	**Year**	**Treatment arms**	**Patients R / A**	**Analysis reviewed by**
Niewald (39), Germany	1996	20Gy /5F vs. 30Gy /15F	100 / 100	Wu, Ratanatharathorn, McQuay
Rasmusson (40), Denmark	1995	15Gy /3F vs. 30Gy /10F	217 / 217	Wu, Ratanatharathorn, McQuay
Hirokawa (41), Japan	1988	25Gy /5F vs. 30Gy /10F	128 / 128	Wu, McQuay
Okawa (42), Japan	1988	20Gy /10F (b.i.d.) vs. 22.5Gy /5F vs. 30Gy /15F	80 / 80	Wu, Ratanatharathorn, Ben-Jozef, Mc
Blitzer (43), USA‡	1995	-	-	-
Madsen (44), Denmark	1983	20Gy /2F vs. 24Gy /6F	266 / 146	Wu, Ratanatharathorn, Ben-Jozef, Mc
Tong (45), USA	1982	Solitary metastasis 40Gy /15F vs. 20Gy /5F		Wu, Ratanatharathorn, Ben-Jozef, Mc
		Multiple metastases 15Gy /5F vs. 20Gy /5F, vs. 25Gy /5F vs. 30Gy /10F	750 / 613	
Trials comparing different single fraction regimens				
Author/country	**Year**	**Treatment arms**	**Patients R / A**	**Analysis reviewed by**
Jeremic (46), Yugoslavia	1998	4Gy vs. 6Gy vs. 8Gy	327 / 327	Wu, Ratanatharathorn
Hoskin (47), UK	1992	4Gy vs. 8Gy	270 / 196	Wu, Ratanatharathorn, Ben-Jozef, Mc

* *R= number of patients randomized, A= number of patients assessable for response calculations. NS= not stated*

† *This publication was a further analysis of the Dutch Bone Metastasis Study by Steenland et al, correcting for the infl uenc and changes in analgesics intake*

‡ *This publication was a reanalysis of the RTOG 74-02 trial by Tong et al*

effi cacy between different fractionation schedules, nor of a dose response correlation with total dose of radiation. [6] These three systematic reviews, however, did not include the three large trials that were published since 1998 which all showed the equal effectiveness of single and multiple fractions, with the Dutch Bone Metastasis Study being the largest trial to date . [2,7,8] A smaller fourth study by Kirkbride et al with equal responses in 278 patients between 8 Gy SF and 20 Gy in 5 fractions was presented at the annual meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO) in 2000, but the full paper has not been published as of yet.[9]

In 2003, Wu et al [10] published an impressive quantitative meta-analysis on 16 trials and concluded that single dose radiotherapy was as effective as multiple fractions for the majority of patients with painful bone metastases *(Figures 1 and 2)*. A systematic review by Sze et al concluded similarly. [11]
There are three randomized trials on bone metastases which reported only preliminary results so far. The RTOG 97-14 study, presented at the annual ASTRO meeting in October 2003, could not rule out the equal effectiveness of 8 Gy SF versus 30 Gy in 10 fractions in a group of 897 patients. [12] More de fi nitive results on durability of response in this trial have to be awaited for. Recently, Foro Arnalot et al reported at the 2004 ESTRO meeting on the equal effectiveness of 8 Gy single fraction vs 30 Gy in 10 fractions in 160 patients. [4] Early results of the last ongoing Australian trial TROG 97.14 for neuropathic pain, i.e. pain with a radiating cutaneous component due to compression or irritation of nerves by tumor, reported effectiveness of radiotherapy in 60% after 8 Gy SF and 20 Gy MF radiotherapy. [13] The fi nal results will be presented in the near future.

By now, we think the radiotherapy community will have to conclude that the literature on the equal effectiveness of a single dose schedule versus more protracted regimens for the majority of patients with painful bone metastases is overwhelming.[14,15]

URE 1

Meta-analysis of complete response rates from randomized trials of single vs. multiple fractions of RT for painful bone metastases (intention-to-treat); n= number of patients achieving complete response; N= number of patients randomized

dy	Single n/H	Multiple n/H	RR (95% CI Random)	RR (95% CI Random)
adian 2000	44/200	57/198		0.76(0.54,1.07)
e Pain Trial 1999	199/383	192/378		1.02(0.89,1.17)
ch 1999	199/585	175/586		1.14(0.96,1.35)
vig 1998	16/52	18/55		0.94(0.54,1.64)
sen 1998	18/119	21/122		0.88(0.49,1.56)
e 1997	50/134	47/131		1.04(0.76,1.43)
e 1986	13/140	13/148		1.06(0.51,2.20)
l (95% CI)	539/1613	523/1618		1.03(0.94,1.13)

for heterogeinity chi-square=4.75 df=6 p=0.58
for overal effect z=0.62 p=0.5

Favors multiple Favors single

Meta-analysis of overall response rates from randomized trials of single vs. multiple fractions of RT in painful bone metastases (intention-to-treat)); n= number of patients achieving complete or partial response; N= number of patients randomized

dy	Single n/H	Multiple n/H	RR (95% CI Random)	RR (95% CI Random)
adian 2000	101/200	95/198		1.05(0.86,1.29)
e Pain Trial 1999	274/383	257/378		1.05(0.96,1.16)
ch 1999	392/585	361/586		1.09(1.00,1.18)
sen 1998	52/119	56/122		0.95(0.72,1.16)
vig 1998	41/52	45/55		0.96(0.80,1.16)
e 1997	108/134	99/131		1.07(0.94,1.21)
1989	14/16	11/13		1.03(0.77,1.39)
e 1986	29/140	34/148		0.90(0.58,1.40)
l (95% CI)	1011/1629	958/1631		1.05(1.00,1.11)

for heterogeinity chi-square=2.44 df=7 p=0.93
for overal effect z=2.04 p=004

Favors multiple Favors single

FIGURE 2

(a) Sensitivity analysis using assessable patients as denominators for complete response rates, single vs. multiple fractions; n= number of patients achieving a complete response; N= number of patients assessable

Study	Single n/H	Multiple n/H	RR (95% CI Random)	RR (95% CI Random
Canadian 2000	44/143	57/135		0.73(0.53,1.00)
Bone Pain Trial 1999	199/351	192/330		0.97(0.86,1.11)
Dutch 1999	199/545	175/528		1.10(0.93,1.30)
Nielsen 1998	18/106	21/101		0.82(0.46,1.44)
Koswig 1998	16/52	18/55		0.94(0.54,1.64)
Gaze 1997	50/129	47/111		0.92(0.67,1.24)
Price 1986	13/9	13/48		0.98(0.51,1.89)
Total (95% CI)	539/1375	523/1308		0.98 (0.89,1.07)

Test for heterogeinity chi-square=5.96 df=6 p=0.43
Test for overal effect z=0.51 p=06

Favors multiple Favors single

(b) Sensitivity analysis using assessable patients as denominators for overall response rates, single vs. multiple fractions; n= num of patients achieving overall response; N= number of patients assessable

Study	Single n/H	Multiple n/H	RR (95% CI Random)	RR (95% CI Random
Canadian 2000	101/143	95/135		1.00(0.86,1.17)
Bone Pain Trial 1999	274/351	257/330		1.00(0.93,1.09)
Dutch 1999	392/545	361/528		1.05(0.97,1.14)
Nielsen 1998	52/106	56/101		0.88(0.68,1.15)
Koswig 1998	41/52	45/55		0.96(0.80,1.16)
Gaze 1997	108/129	99/111		0.94(0.85,1.04)
Cole 1989	14/16	11/13		1.03(0.77,1.39)
Price 1986	29/49	34/48		0.84(0.62,1.12)
Total (95% CI)	1011/1391	958/1321		1.00(0.95,1.04)

Test for heterogeinity chi-square=5.63 df=7 p=0.58
Test for overal effect z=0.17 p=09

Favors multiple Favors single

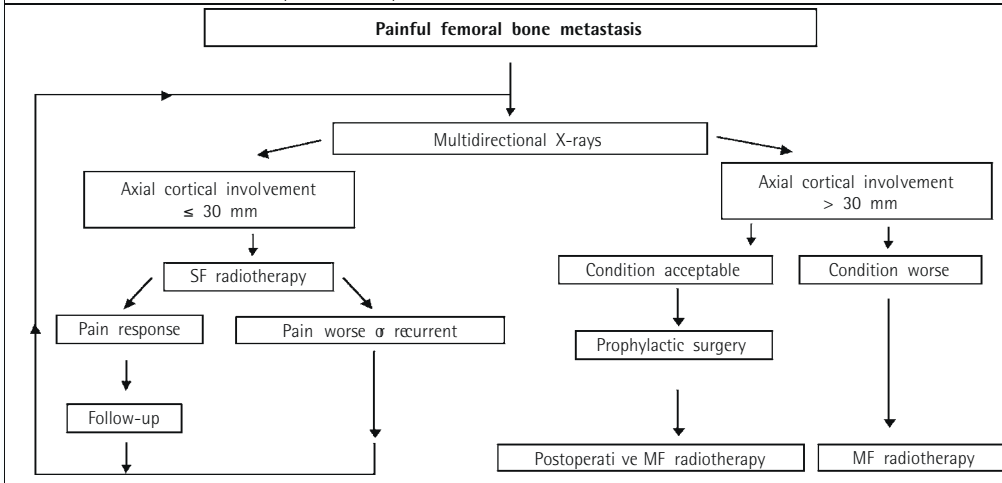
Implementation of the single dose schedule for painful bone metastases.
One could argue that single fraction radiotherapy would by now have become the standard therapy in the world, but unfortunately this is not the case.[16-18] In **chapter 2** an editorial is presented concerning this topic. Besides clinical arguments, socio-economic factors also affect the choice for a specifi c treatment. Lievens et al published two articles on the subject of reimbursement.[19,20] Long schedules were predominantly seen amongst the Western European centres when fee-for-service was the type of reimbursement, and single fractions prevailed in budget and/or case payment systems. In the Netherlands, which has a case payment system, we conducted a sur - vey among all 21 radiotherapy departments after the global analysis of the DBMS was published in September 1999 by Steenland et al. [2] Almost all Dutch institutions converted to the single fraction regimen for the majority of patients with painful bone metastases (data not shown). In **chapter 9** willingness-to-pay was introduced as a method to decide on palliative treatment. We demonstrated that the single fraction regimen was superior for all willingness-to-pay values less than $40000. This implicates that for the Netherlands, the SF regimen is a proven cost effective treatment for patients with painful bone metastases.
Clinical arguments for hesitation to implement the single dose schedule were the higher retreatment rates after SF, scepticism on the effectiveness of a SF in patients with an expected prolonged survival, the higher risk of sustaining a fracture after SF, and patient preference for the multiple fraction regimen.[10,11,15,21] However, the analyses of the DBMS database presented in this thesis were able to rebut most of these arguments:

Retreatment of bone metastases: effectiveness and optimal dose-fractionation schedule
In **chapter 4** the results were presented from a reanalysis of the DBMS in alignment with the international guidelines on bone metastases trials, [1] separating the infl uence of a retreatment on the initial response calculations, and incorporating possible changes in analgesics intake. We showed that response percentages between both treatment schedules were equal even with the effect of a retreatment excluded from the response calculations. In addition, we demonstrated that physicians were more willing to retreat a patient if the initial treatment was a SF. Because the published trials did not include protocol guidelines for retreatment, the higher retreatment percentages after a SF reported in the literature were biased. [10] To answer all outstanding questions on retreatment, the fi rst randomized trial on the effect of retreatment in bone metastases using different dose schedules was started in 2004, initiated by the National Cancer Institute of Canada (NCIC CTG SC20). This trial randomizes between 8 Gy SF or 20 Gy MF, and is designed as an international multicenter study. The study is planning to accrue 650 patients in three years.

Effect of radiotherapy in patients with a prolonged survival
In the global analysis of the DBMS (see appendix 1), Steenland et al already reported on a subgroup of 92 patients with an expected favorable prognosis who had been separately randomized.[2] In these patients, no differences between SF or MF were observed. In **chapter 5** we studied all patients with an observed prolonged survival (> 52 weeks after randomization) and found no differences in response percentages and duration of response between the single dose (87%) and multiple fraction regimen (85%). These 320 long term surviving patients had mostly breast cancer or prostate cancer. We demonstrated that the primary tumor type was the best predictive factor for both survival and response to radiotherapy, with the highest response percentages in patients with breast cancer, followed by prostate cancer **(chapters 4 and 5)** . We believe that the single fraction regimen should also be the standard treatment for patients with an expected prolonged survival (i.e. patients with a good Karnofsky Performance Score, a solitary bone metastasis and no visceral metastases).

Femoral metastases
Chapters 6 and 7 studied the infl uence of lesional characteristics and radiotherapy total dose in patients with femoral lesions. The only lesional characteristic predictive for fracturing was the axial cortical involvement of the lesion with a cut off point at 30 mm. For lesions with an axial cortical involvement

FIGURE 3
Decision tree for the treatment of patients with painful bone metastases of the femur.



smaller than 30 mm a SF was as safe as multiple fractions. We therefore propose a decision tree for the treatment of femoral lesions *(figure 3)*. Although application of this decision tree will lead to a certain degree of surgical overtreatment, the morbidity of sustaining a pathological fracture is considered very traumatic for the patient. [22] From an economic perspective, pathological fracturing is costly; a recent study showed high direct costs in older women who fractured a bone.[23]

Most prognostic factors to select impending lesions, including the axial cortical involvement of the lesion, have only limited positive predictive values and lead to surgical overtreatment **(chapter 7)**. Research in order to refine these prognostic factors for fracturing is necessary, because the potential benefit of an intervention in this increasing patient population is promising. In the Netherlands, a research proposal on fracture risks utilizing patient specific computer models (Finite Element Models) based on prospectively patient derived information on daily activities and repetitive CT scanning is currently being developed.

Spinal metastases

In **chapter 8** we showed that patients with Harrington's Class I and II spinal metastases[24] benefit from 8 Gy single fraction radiotherapy. Another relatively uncommon treatment modality for painful spinal metastases is vertebroplasty, i.e. injection of the lesion with polymethylmethacrylate to strengthen the vertebra. In the Netherlands, a prospectively randomized study is under construction that will study the palliative effect of vertebroplasty versus radiotherapy in patients with Harrington' Class I and II lesions.

For patients with Harrington' Class III lesions, the results of a trial were reported at the ASTRO 2003 annual meeting in which 101 patients with spinal cord compression were randomized between decompressive surgery followed by radiotherapy or radiotherapy alone. [25] After an interim analysis, the stopping rule was met because neurological outcome was in favour of the surgery arm. Patients treated with surgery + radiotherapy retained the ability to walk significantly longer than those treated with RT alone (median 126 days vs. 35 days, P= 0.006). Although the full paper is not yet published, adjustment of the primary care for these patients needs to be discussed between all oncologists involved, with probably a larger role for decompressive surgery. For patients with Harrington' Class III lesions and a low performance status, and/or short life expectancy, an interim analysis of a randomized radiotherapy trial on hypofractionation was recently presented at ESTRO 2004.[26] Patients were randomized between 8 Gy SF or 2 fractions of 8 Gy. In 82 patients no differences in response or toxicity were seen, with relief of back pain in 65%, ability to walk in 76%, and good bladder function in 81% of the patients. The final results of this trial will be presented in a few years time.

In the near future, intensity modulated radiotherapy will enable retreatment of spinal metastases. [27] With this highly innovative technique, sparing of the spinal cord enlarges the dose that can be applied safely to the vertebra without damaging the adjacent spinal cord with high total doses of irradiation.

Health-related quality of life

Particularly in the palliative setting, health-related quality of life is considered more and more as an important treatment outcome. [28] In the DBMS, the follow up questionnaires contained quality of life related issues on complaints and side-effects using the EORTC QLQ C30 questions,[29] and the Rotterdam Symptom Check List.[30] Overall quality of life was studied using a Visual Analogue Scale, a 7-point overall valuation of life scale, and the EuroQOL 5D questionnaire. [31] Although no differences in treatment side effects and overall quality of life in the two randomization groups were found, as was mentioned in **chapters 3, 9** and in **appendix 1**, in-depth analyses on quality of life still have to be performed by the DBMS group. However, we presume that the QOL instruments used in the DBMS are probably not specific enough to detect subtle differences. Local radiotherapy may improve activities of daily living that are hampered by bone pain, but not improve overall quality of life in patients burdened with a systemic disease. A specific bone metastases module on patient-defined activity interference to accompany the EORTC QLQ-C30 questionnaire for future clinical trials in patients with bone metastases is currently under development.

Final conclusion

The outcome of the Dutch Bone Metastasis Study clearly shows that a single fraction of 8 Gy is as effective as 24 Gy in 6 fractions in treating painful bone metastases from solid tumors. A single fraction of 8 Gy should be the standard therapy for the vast majority of patients with painful bone metastases.

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Summar y / Samen vatting