Risk factors for survival of 106 surgically treated patients with symptomatic spinal epidural metastases

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Received: 28 September 2012 / Revised: 1 February 2013 / Accepted: 18 February 2013 / Published online: 2 March 2013
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Abstract

Purpose Evaluation of risk factors for survival in patients surgically treated for symptomatic spinal epidural metastases (SEM).

Methods One hundred and six patients who were surgically treated for symptomatic SEM in a 10-year period in two cooperatively working hospitals were retrospectively studied for nine risk factors: age, gender, site of the primary tumor, location of the symptomatic spinal metastasis, functional and neurologic status, the presence of visceral metastases and the presence of other spinal and extraspinal bone metastases. Analysis was performed using the Kaplan–Meier method, univariate log-rank tests and Cox-regression models.

Results Overall median survival was 10.7 months (0.2–107.5 months). Overall 30-day complication rate was 33 %. Multivariate Cox-regression analysis showed that

fast growing primary tumors (HR 3.1, 95 % CI 1.6–6.2, $p = 0.001$), the presence of visceral metastases (HR 1.7, 95 % CI 1.0–2.9, $p = 0.033$) and a low performance status (HR 2.7, 95 % CI 1.1–6.6, $p = 0.025$) negatively influenced the survival.

Conclusion Primary tumor type, presence of visceral metastases and performance status are significant predictors for survival after surgery for symptomatic SEM and should be evaluated before deciding on the extent of treatment. More accurate prediction models are needed to select the best treatment option for the individual patient.

Keywords Spinal metastasis · Spinal metastases · Risk factors · Survival

Introduction

Symptomatic spinal epidural metastases (SEM) continue to be a disabling consequence of cancer, causing a decrease in quality of life due to pain and neurological decline. With the development of better treatment options for the primary cancer, survival periods in metastatic disease will increase and will most likely lead to a rise in the incidence of metastatic spine disease. There is consensus on the fact that surgery can be beneficial to patients presenting with SEM [1–3]; however, the optimal type of surgery to be used on an individual patient remains unclear. The goals of surgical intervention are to relieve pain and neurologic deficit by decompression of the spinal cord or cauda equina and stabilization of the spine. Surgical strategies to achieve these goals vary greatly in extent of tumor removal (ranging from debulking to en bloc resection of the affected vertebra) and type of stabilization (ranging from none to circumferential reconstruction with vertebral body

Part of the Leiden—The Hague Spinal Intervention Prognostic Study (SIPS) group.

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replacement). Secondary to open surgery, minimal invasive techniques such as percutaneous vertebroplasty (PVP) or kyphoplasty and percutaneous pedicle screw fixation are increasingly used.

In practice, the surgeon will match the type of surgery to the expected survival time, thus balancing the increase in morbidity associated with more extensive surgery to the expected gain in quality of life and mobility.

Models to aid in the selection of surgical candidates have been developed by Tokuhashi et al. [4, 5], Tomita et al. [6], van der Linden et al. [7] and Bauer and Wedin [8]. Disadvantages of these models are that they vary in the amount and type of risk factors used (see Table 1) and the weight assigned to each of these factors, resulting in different scores for the same patient. Also, patient populations on which the models are based differ greatly; van der Linden used data of radiation therapy patients only and Bauer based his model on a mixed group of patients with bone metastases to the extremities as well as the spine. As a consequence, the use of such a model entails a risk of over or under treatment and clinical applicability is limited.

Since life expectancy is of such great influence on therapeutic decision-making, its accurate prediction is of the utmost importance.

The goal of this study is to retrospectively identify clinically relevant risk factors for estimating survival in 106 patients who were surgically treated in a 10-year period at our two centers.

Materials and methods

Patients

All patients who were surgically treated for symptomatic SEM between January 2001 and December 2010 by one surgical team in two tertiary referral centers in the

Netherlands were included. Forty-seven patients were operated at the Leiden University Medical Center and 59 at the Medical Center Haaglanden. The surgical team performed the spinal interventions in both hospitals. Surgical treatment was defined as all invasive procedures, aimed at palliation or control of symptoms of SEM. These procedures consisted of percutaneous vertebroplasty, intraleSIONAL decompression, partial or complete corpectomy and a single en bloc resection, either through an anterior, posterior or combined approach. Choice of technique and approach were dependent on location of the metastasis, possibilities of fixation on adjacent levels, expected survival and surgeon preference.

Table 2 shows all baseline characteristics of the study population. One patient died during surgery due to myocardial infarction and was excluded from the analysis. For reasons of completeness, the patient is mentioned in the complication summary. A total of 106 patients were included in the study, 53 males and 53 females. The mean age at surgery was 59.0 years. The most commonly affected part of the spine was the thoracic region (56 %). During the course of treatment for the symptomatic SEM, 9 patients underwent systemic treatment (i.e. chemotherapy and/or hormone therapy), 31 patients received radiation therapy, and 55 patients received both. Thirty patients had radiation therapy preoperatively and 56 postoperatively. Forty-seven patients had no sign of neurologic deficit, indicating they were referred either for persisting pain, a

Table 1 Six risk factors used in the four predictive models

	Tomita	Tokuhashi (revised)	van der Linden	Bauer (modified)
Primary tumor	×	×	×	×
Karnofsky performance status		×	×	
Visceral metastases	×	×	×	×
Extraspinal bone metastases	×	×		×
Number spinal metastases	×	×		×
Frankel classification		×		

Table 2 Patient characteristics

Characteristics	Number (%)
Gender	
Male	53 (50)
Female	53 (50)
Age (mean, years, SD)	59.0 ± 10.9
Center	
LUMC	47 (44)
MCH	59 (56)
Location symptomatic spinal metastasis	
Cervical	23 (22)
Thoracic	60 (56)
Lumbar	23 (22)
Adjuvant therapy SEM, perioperatively	
None	11 (10)
Systemic therapy	9 (9)
Radiation therapy	31 (29)
Both	55 (52)
Neurologic deficit	
No (Frankel grade E)	47 (44)
Yes (Frankel grade A, B, C, D)	59 (56)

SD standard deviation

Table 3 Primary tumors and median survival for each primary

Primary tumor	Number (%)	Median survival (95 % CI)
Breast	25 (23)	34.7 (11.8–46.8)
Lung	20 (18)	6.9 (0.0–21.6)
Kidney	19 (18)	14.9 (7.2–22.8)
Prostate	11 (10)	9.2 (1.2–16.8)
Colon	6 (6)	1.7 (0.0–13.2)
Sarcomas	5 (5)	8.8 (4.8–13.2)
Melanoma	4 (4)	3.4 (0.0–7.2)
Thyroid	3 (3)	35.6 ^a (–)
Rectum	2 (2)	2.1 (–)
Esophagus	2 (2)	3.9 (–)
Pharynx	2 (2)	7.2 (–)
Other	7 (7)	2.7 (1.2–3.6)

^a Median could not be calculated, mean is given

pathologic fracture or for instability of the spinal column. The most prevalent primary tumors were breast ($n = 25$), lung ($n = 20$), kidney ($n = 19$) and prostate ($n = 11$) (see Table 3).

Seven patients underwent percutaneous vertebroplasty, 46 had limited posterior decompressive surgery and 52 patients had extended decompressive surgery in the form of an intralesional corpectomy. One patient was treated with an en bloc resection (see Table 4).

Risk factors

All available patient records were retrospectively studied for gender, age, site of the primary tumor, location of the symptomatic spinal metastasis, preoperative functioning according to the Karnofsky performance status (KPS) [9, 10], the presence of visceral metastases, the presence of other spinal and extraspinal bone metastases and neurologic functioning according to the Frankel classification [11]. Based on the survival data from this study, the primary tumor scores of the Tomita and van der Linden models were adapted to better reflect the study population: in the van der Linden model, kidney cancer was added to the ‘prostate group’ and thyroid cancer was added to the ‘breast group’. In the Tomita model, prostate cancer was moved to the ‘moderate growth’ category. KPS was scored in the period leading to surgery and not shortly before, to avoid the influence of acute neurologic decline. Date of surgery, date of complications and date of death were obtained from medical records or from general practitioners.

Statistical analysis

Survival time was calculated as the difference in months between date of surgery and date of death or last follow-up,

Table 4 Surgical details

Surgical details	Number (%)
Type of surgery	
Percutaneous vertebroplasty	7 (7)
Decompression w/o fixation	24 (22)
Decompression with fixation	22 (21)
Partial corpectomy	12 (11)
Complete corpectomy	40 (38)
En bloc resection	1 (1)
Approach	
Posterior	86 (81)
Anterior	11 (10)
Combined	9 (9)
Means of stabilization ^a	
No additional stabilization	24 (24)
Pedicle screws/rods	30 (30)
Cage with additional fixation	45 (46)

^a Patients treated with percutaneous vertebroplasty excluded

with a minimum follow-up of 11 months. Survival curves were estimated using the Kaplan–Meier method. Influence of the risk factors was assessed by employing log-rank tests for univariate analysis, and for multivariate Cox analysis, a backward stepwise procedure was used. A p value of <0.05 was considered statistically significant. All analyses were performed using SPSS 18.0, SPSS Inc., Chicago, IL, USA.

Results

Survival

The overall median survival was 10.7 months (0.2–107.5 months) (see Fig. 1). Eighty patients (75 %) died during follow-up, with a median survival of 6.5 months (0.2–106.8 months). Twenty-five patients (24 %) died within 3 months after surgery and 13 patients (12 %) died 3–6 months after surgery.

The highest median survival time was found in patients with breast cancer (34.7 months), followed by kidney (14.9 months) and prostate cancer (9.3 months). Patients with colon cancer had the lowest median survival (1.7 months).

Complications

Within 30 days after surgery, 35 patients (33 %) had one or more complication with a total of 53 recorded complications. Nine patients had multiple complications. The most common were wound infection ($n = 8$), new minor neurologic deficits such as radicular pain or reduced sensibility

Fig. 1 Overall survival

($n = 8$), cerebrospinal fluid leak ($n = 6$), and pneumonia ($n = 4$) (see Table 5). Three patients had to be reoperated due to instrumentation failure or acute neurologic decline. Ten patients died within 30 days, mostly due to systemic complications such as sepsis and respiratory failure. The complication rate in this group was 70 %.

Univariate analysis of risk factors

Results for the univariate analysis are shown in Table 6 and Figs. 2, 3, 4. All primary tumor classifications were significant predictors for survival after surgery. However, none of the classifications were able to systematically differentiate between all of their subgroups (see “Appendix”). The absence of visceral metastases ($p = 0.014$) had a significant effect on survival. Gender, location of the symptomatic spinal metastasis, number of spinal metastases, presence of other bone metastases, age, KPS and Frankel classification had no effect on survival after surgery.

Multivariate analysis of risk factors

A multivariate Cox-regression analysis was performed by employing as risk factors primary tumor (Tomita modified, moderate growth HR 1.7, 95 % CI 0.9–3.3, $p = 0.099$; fast growth HR 3.1, 95 % CI 1.6–6.2, $p = 0.001$), presence of visceral metastases (HR 1.7, 95 % CI 1.0–2.9, $p = 0.033$) and performance status (KPS 50–70 HR 1.3, 95 % CI 0.8–2.1, $p = 0.292$; KPS 10–40 HR 2.7, 95 % CI 1.1–6.6, $p = 0.025$) (see Table 7).

Table 5 30-day complications

Complication	Number (%)
Cardiac	
Myocardial infarction ^a	1 (2)
Arrhythmia	2 (4)
Extensive blood loss	1 (2)
Gastrointestinal	
Ileus	1 (2)
Bleed	1 (2)
Infection	
Pneumonia	4 (8)
Sepsis	2 (4)
Neurologic	
New minor deficits	8 (15)
New major deficits	2 (4)
Delirium	3 (6)
Pulmonary	
Respiratory failure	2 (4)
Pleural empyema	1 (2)
Renal	
Acute renal failure	1 (2)
Metabolic	
Hyponatremia	1 (2)
Metabolic acidosis	1 (2)
Skeletal	
Pathologic fracture	1 (2)
Surgical site	
Wound infection	8 (15)
Wound dehiscence	1 (2)
Wound leakage	1 (2)
Hematoma	2 (4)
Cerebrospinal fluid leak	6 (11)
Instrumentation failure	3 (6)

^a Death occurred during surgery

Discussion

In this study on 106 patients operated for symptomatic SEM, primary tumor type, presence of visceral metastases and functional status were found to be significant predictors of survival. Other risk factors such as gender, presence of other bone metastases, number and location of spinal metastases, age and neurologic status did not have an effect on survival.

For the purpose of accurately evaluating the individual risk factors, modifications to two items were made.

We agree with Wibmer et al. [12] that the primary tumor classifications are not up to date. However, based on survival data in this study, the conclusion that patients suffering from kidney cancer have a prognosis comparable to those with breast cancer cannot be followed. Median

Table 6 Results of univariate analysis

Univariate analysis	<i>p</i> value
Primary tumor classification	
Tomita (modified)	<0.001
Tokuhashi (revised)	0.001
van der Linden (modified)	0.002
Bauer (modified)	0.008
Karnofsky performance status	
100–80/70–50/40–10	0.169
Visceral metastases	
Present/removable/unremovable	0.027
Present/not present	0.014
Bone metastases	
Solitary/multiple ^a	0.946
0/1–2/≥3	0.970
Number of spinal metastases	
1/2/≥3	0.860
Frankel classification	
A + B/C + D/E	0.196
Age	
<65/≥65	0.089
Location	
C-Th6/Th7-L	0.163
Gender	
Male/female	0.159

^a Including spinal metastases

Fig. 2 Primary tumor classification Tomita modified

survival in patients with prostate cancer was compatible with the 'moderate growth' category in the Tomita model, and therefore it was decided to remove it from the 'slow

Fig. 3 Visceral metastases **Fig. 4** Karnofsky performance status

growth' category. In 2004, van der Linden et al. [7] studied 342 patients with spinal metastases who were conservatively treated for pain by means of external beam radiation therapy. Since patients with renal cell carcinoma were excluded and patients with thyroid cancer were under-represented, these primary tumors are not mentioned separately in the model. Scoring these tumors in the 'other' category is incorrect and adjustments are needed: kidney

Table 7 Results of multivariate Cox-regression analysis

Multivariate analysis	HR	<i>p</i> value	95 % CI
Tomita primary tumor classification			
Slow	1.7	0.004	0.9–3.3
Moderate	3.1	0.099	1.6–6.2
Fast		0.001	
Visceral metastasis			
Present/not present	1.7	0.033	1.0–2.9
Karnofsky performance status			
80–100		0.077	
50–70	1.3	0.292	0.8–2.1
40–10	2.7	0.025	1.1–6.6

HR hazard ratio, 95 % CI 95 % confidence interval

cancer was added to the ‘prostate group’ and thyroid cancer was added to the ‘breast group’.

The preoperative assessment of the Karnofsky performance score was standardized. In a patient population notoriously at risk for acute neurologic decline, we believe it is wrong to take such a measurement just prior to surgery because of the acute distorting effect of neurologic impairment on functional impairment. Therefore, it was decided by the authors that functional status had to be evaluated before the onset of acute neurologic decline.

When assessing primary tumor type, the Tomita classification was found to be the most practical and—after modification—also the most accurate of the four classifications. The difference in survival between slow and moderate growth tumors is not significant on both univariate ($p = 0.073$) and multivariate analyses (HR 1.7, 95 % CI 0.9–3.3, $p = 0.099$), but the difference between slow and fast growth ($p < 0.001$) and moderate and fast growth ($p = 0.007$) is strongly significant.

Even though the results of the van der Linden classification improved after modification, accuracy is still lacking, as is the case for the Tokuhashi and Bauer classifications. An explanation for this finding may be the relatively long survival of patients with lung cancer in this study (median survival 6.9 months). Bias might have been introduced by selection of only those lung cancer patients with preoperative estimated long survival. Whereas in the Tomita classification, this primary is mixed with other fast growing tumors such as melanoma (median survival 3.4 months) and colon cancer (median survival 1.7 months), the other classifications use this primary as a separate entity. This underlines another advantage of the Tomita tumor classification: its adaptability. We believe it is impossible to present a globally valid tumor classification, considering the differences in incidences and ever-changing treatment options. By creating categories based on contemporary regional survival data, results will be more accurate than

when adhering to semi-rigid classifications as presented in other classifications.

As a marker for progression of disease, the presence of visceral metastases does not directly influence survival. In their models, Tomita and Tokuhashi make use of a third category, namely operability. Tokuhashi et al. [4] initially based this category on a single patient out of the 64 studied and Tomita et al. [6] on 7 out of 67 patients. As is shown in the results, operable visceral metastases have a similar median survival when compared to no visceral metastases. Unfortunately, the treatable visceral metastases group only consisted of six patients. These results are most likely due to patient selection. If a patient is considered fit enough to undergo metastasectomy, survival will most likely be prolonged based on their general condition and not the removal of the visceral metastasis. A recent retrospective study of 504 breast cancer patients irradiated for metastatic spinal cord compression by Rades et al. [13] also found a strong negative effect on survival if visceral metastases were present, similar to Wibmer et al. [12], Yamashita et al. [14] and Crnalic et al. [15].

Performance status is generally accepted as a strong prognostic factor for survival in metastatic disease [16], but in case of spinal metastases, it remains controversial. Even though both the Tokuhashi and the van der Linden models make use of the KPS, evidence is still limited. In his article, Tokuhashi writes: “(...) the standard deviation was too great for the values to be sufficiently meaningful [4]”.

Pointillart et al. [17] found the KPS to be a significant predictor of survival on univariate analysis, but unfortunately did not perform an analysis for each category. In their study, the HR was equal to 0.98 ($p = 0.002$, 95 % CI 0.96–0.99), indicating that performance status was not clinically relevant.

In a retrospective study, evaluation of performance status is challenging, especially when trying to avoid the influence of neurologic deficit. The data suggest an effect of performance status on survival, but only on multivariate analysis and when divided in three groups. The HR for a KPS score 50–70 is equal to 1.3 ($p = 0.292$, 95 % CI 0.8–2.1), but the HR for a KPS score 10–40 is equal to 2.7 ($p = 0.025$, 95 % CI 1.1–6.6).

Chi et al. [18] considered the effects of age in predicting survival as well as preservation of ambulation for patients treated for spinal metastases. We agree that particular age cutoff points can help in selecting patients, but did not find their suggested age of 65 to be accurate in this population ($p = 0.089$).

Neurologic deficit has no significant effect on survival ($p = 0.196$), stressing that this variable should be excluded when evaluating performance status. Even though survival is not affected by neurologic functioning, it is an important factor that should be considered when deciding on treatment.

In patients with malignancies, the presence of bone metastases can be used as a marker for progression of disease. However, if a patient is already affected by spinal bone metastases, the presence or absence of extraspinal bone metastases is inconsequential. Neither the classification according to Tokuhashi ($p = 0.970$), nor the classification according to Tomita or Bauer ($p = 0.946$) resulted in a significant effect.

The amount ($p = 0.860$) and location ($p = 0.493$) of spinal metastases have no impact on survival. Similar to neurologic functioning, they, however, have consequences when deciding on treatment. Feasibility, approach and extent of surgery should be weighed against amount of metastatic involvement of the spinal column and location of the symptomatic metastases.

Based on these results, it can be argued that there are several flaws in the current scoring systems. First, the primary tumor classifications need to be updated based on larger populations. Our experience is that the Tomita classification is the ideal framework for doing so. Second, several risk factors should be removed from the models. Other bone metastases, number of spinal metastases and neurologic deficit are all important factors to consider when deciding on surgery, but do not play a role in estimating survival. Finally, provided neurologic deficit is excluded as a confounder, functional status should be included in any scoring system, as should the presence of visceral metastases. Currently, the only model to contain these risk factors, without the drawback of having to evaluate several others, is the van der Linden model. If the primary tumor classification would be revised, preferably along the lines of the classification proposed by Tomita, this model would be superior in ease of use as well as accuracy.

Even though estimating survival is an important part of the decision-making process concerning the treatment of symptomatic SEM, it should never be the only point of interest. Neurologic symptoms and their duration, pain, feasibility of other treatment options, stability of the spinal column and expected gain in quality of life should all be discussed, preferably in a multidisciplinary setting [19].

Complication rate in this study is high (33 %). This is mainly due to the fact that only surgically treated patients

were included and that surgical techniques used were aggressive (50 % partial or complete corpectomy).

A limitation of this study is its retrospective design and the fact that only surgically treated patients are evaluated. Therefore, patients who were referred for surgical consultation but did not receive treatment are not represented in this study. The wide array of surgical interventions used is due to the lack of clinical guidelines during the period described in this study. Also, the heterogeneity of primary tumors can cause discrepancies in recorded survival times of the smaller groups when compared with other studies.

Primary tumor type, presence of visceral metastases and functional status are strong risk factors for determining survival in patients operated for symptomatic spinal epidural metastases and should always be carefully evaluated.

Acknowledgments The authors would like to thank D.J. Lobatto and W.S.F.J. Tummers for their invaluable support in creating the database.

Conflict of interest None of the authors have a conflict of interest to declare.

Appendix

If a risk factor is divided into more than two categories, pairwise grouped analysis was performed using log-rank tests. Data presented are p values. For each category, number of patients and median survival in months with 95 % confidence interval is given (see Tables 8, 9, 10, 11, 12, 13, 14, 15, 16).

Table 8 Grouped analysis modified Tomita primary tumor classification

Primary Tomita (modified)	Slow	Moderate	Fast	Median survival
Slow	28	0.073	<0.001	39.0 (21.6–56.4)
Moderate	37		0.007	11.5 (4.3–19.2)
Fast	41			3.9 (0.1–7.8)

Table 9 Grouped analysis revised Tokuhashi primary tumor classification

Primary Tokuhashi (rev.)	Breast, etc.	Rectum	Kidney, etc.	Other	Liver, etc.	Lung, etc.	Median survival
Breast, etc.	39	0.054	0.131	0.029	<0.001	<0.001	34.7 (20.4–49.2)
Rectum	2		0.437	0.775	0.277	0.797	2.1 (–)
Kidney, etc.	19			0.568	0.021	0.115	14.9 (7.2–22.6)
Other	20				0.020	0.503	6.8 (5.3–8.3)
Liver, etc.	3					0.151	2.0 (2.0–2.1)
Lung, etc.	23						6.9 (0.5–13.3)

Table 10 Grouped analysis modified van der Linden primary tumor classification

Primary van der Linden (modif.)	Breast, etc.	Kidney, etc.	Lung	Other	Median survival
Breast, etc.	28	0.030	<0.001	0.001	39.0 (21.6–56.4)
Kidney, etc.	31		0.142	0.273	11.5 (3.1–19.9)
Lung	21			0.844	6.9 (0.0–18.6)
Other	26				6.5 (3.2–9.8)

Table 11 Grouped analysis modified Bauer primary tumor classification

Primary Bauer (modified)	Breast, etc.	Other	Lung	Median survival
Breast, etc.	44	0.041	<0.001	29.1 (19.4–38.8)
Other	41		0.431	7.1 (4.3–9.9)
Lung	21			6.9 (0.0–18.6)

Table 12 Grouped analysis Tokuhashi/van der Linden Karnofsky performance status classification

KPS	100–80 %	70–50 %	40–10 %	Median survival
100–80 %	47	0.308	0.083	16.8 (5.6–28.1)
70–50 %	47		0.207	10.5 (1.9–19.2)
40–10 %	9			4.3 (0.0–13.4)

Table 13 Grouped analysis Tomita/Tokuhashi visceral metastases classification

Visceral metastases	Removable	Unremovable	None present	Median survival
Removable	6	0.311	0.663	14.9 (5.2–24.5)
Unremovable	28		0.008	6.5 (2.3–10.7)
None present	72			14.9 (1.8–27.6)

Table 14 Grouped analysis Tokuhashi extraspinal bone metastases classification

Bone metastases	0	1–2	≥3	Median survival
0	12	0.852	0.936	11.4 (5.6–17.3)
1–2	14		0.753	7.7 (0.0–18.3)
≥3	80			7.3 (0.0–31.9)

Table 15 Grouped analysis Tokuhashi spinal metastases classification

Spinal metastases	1	2	≥3	Median survival
1	63	0.735	0.748	12.9 (5.9–20.0)
2	23		0.669	11.4 (3.7–19.2)
≥3	20			7.1 (5.3–8.9)

Table 16 Grouped analysis Tokuhashi Frankel classification

Frankel classification	A and B	C and D	E	Median survival
A and B	9	0.111	0.080	3.6 (0.0–8.5)
C and D	50		0.875	7.7 (1.0–14.3)
E	47			15.8 (5.1–26.5)

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