PAIN

Pain 69 (1997) 131–135

Pain characteristics help to predict the analgesic efficacy of radiotherapy for the treatment of cancer pain

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Received 30 August 1995; revised version received 5 September 1996; accepted 5 September 1996

Abstract

It is recognised that radiotherapy provides relief for intractable pain in approximately 50% of patients with cancer pain. Unfortunately, traditional explanatory variables, such as age, gender, histology or radiation dose, do not help to predict which individuals will benefit from palliative radiotherapy. A non-randomised prospective clinical trial was conducted on 51 patients to evaluate the value of pain characteristics as new explanatory variables for predicting the efficacy of palliative radiotherapy for providing cancer pain relief. Two new explanatory variables were identified: the presence of radiating pain and the pain score before radiotherapy.

Keywords: Pain; Cancer; Radiotherapy; Palliative treatment

1. Introduction

About 40% of patients who are referred for radiotherapy have advanced stage cancer which does not respond to curative treatment (WHO Expert Committee, 1990) and is accompanied by pain (Torpie, 1987). In the literature, there is wide variation in the response rates of patients treated with radiotherapy for pain relief: 77% failure rate (Salazar et al., 1981), 80% overall response rate (Hoskin, 1988) and 50% mean complete response rate (Hoskin, 1988). In view of the prospect of short-term survival, severe pain and the wish to spare such patients the extra burden of ineffective treatment, it is of great importance to be able to predict the response to palliative radiotherapy.

Until now, tumour characteristics (e.g., primary histology, stage, localisation of metastases (Hendrickson et al., 1976; Gilbert et al., 1977; Arcangeli et al., 1989) and the radiotherapy method (e.g., dose and fractionation regimens; Allen et al., 1976; Tong et al., 1982; Madsen, 1983; Blitzer, 1985; Price et al., 1986; Tombolini et al., 1994) have served as explanatory variables for predicting whether radiotherapy will provide pain relief. However, there is little support for the notion that either one of these indices or even tumour shrinkage are related to pain relief by radiotherapy (Torpie, 1987; Hoskin, 1991).

Recently, data from our animal experiments have shown that irradiation inhibits behavioural responses to repeated noxious stimulation (Rutten et al., 1994) and we found evidence to suggest that irradiation modified the processing of pain signals. If the considerations on the mechanisms of effect are also applicable to the human condition of cancer and pain, then the characteristics of pain itself may help to predict whether radiotherapy will be effective.

In a non-randomised prospective clinical study, we evaluated the value of pain characteristics as new explanatory variables for predicting the efficacy of radiotherapy.

2. Patients and methods

Patients with cytological or histological evidence of incurable malignant disease and with pain associated with the primary tumour or a metastasis, who had received palliative treatment for pain at the department of radio-

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0304-3959/97/$17.00
PII S0304-3959(96)03253-8

therapy of the University Hospital Nijmegen were selected for the purpose of this prospective study ($n = 75$). Exclusion criteria were younger than 16 years of age, pain not related to the tumour or metastases and an earlier palliative radiotherapy treatment effort for pain relief.

Pretreatment evaluation included registration, an extensive interview and physical examination. Details about the malignant disease, previous therapeutic efforts, pain and the use of analgesics were noted. After receiving a detailed explanation, the patients were asked to fill in a pain questionnaire on a daily basis for 28 days. Recording started on the first day of palliative radiotherapy and the patients handed in their results at weekly intervals. Participants were asked not to modify their medication intake during the evaluation period.

2.1. Radiotherapy

Radiotherapy was applied as an 8 Gy tumour dose in a single fraction or as a 20, 30 or 40 Gy tumour dose in daily fractions of 4, 3 or 2 Gy, respectively. The treatment policy was prescribed by the radiotherapist and was based on the general condition of the patient. A patient with a stable general condition with an imminent fracture was treated with a multi-fraction policy, while patients with a poor general condition were irradiated with a single fraction of 8 Gy.

No adjustments were made for the radiation energy, but when 250 kV X-rays were applied, correction was made for the relative biological effect. Parallel opposing fields were used for the vertebral column, hip, pelvis and long bones; direct fields for the ribs. Doses were prescribed to the mid-plane for parallel opposing fields.

2.2. Measures

Pain intensity was rated on a numeric rating scale (NRS) from 0 to 100 (0 = no pain, 100 = maximum severity). Pain was classified as nociceptive, neurogenic, idiopathic or psychogenic (Merskey and Bugdok, 1994). The efficacy of radiotherapy was classified as complete, partial or no response.

The size of the response was measured by comparing the mean NRS of the first two days of the observation period to the mean NRS of the two last days of the observation period.

Response was defined as complete if full pain relief (NRS = 0) was attained within the evaluation period of 28 days. This response could be achieved at any day during the observation period, and sustained until the end of the observation period. Partial response was defined as a difference of 20 or more between the mean NRS scores recorded on the first two days and the last two days of the observation period, while no response was defined as a difference of less than 20 points.

2.3. Explanatory variables

Four groups of putative explanatory variables were formed: (a) patient characteristics which included age, gender and performance based on the ECOG scale; (b) tumour characteristics which included primary localisation, localisation of metastases, M stage and anti-tumour medication; (c) radiotherapy characteristics which included dose, field size and treatment site; and (d) pain characteristics which included the number of hours that a patient experienced pain (pain hours) divided into two categories of ≤12 h and >12 h, the level of pain before radiotherapy (NRS score), the presence/absence of radiating pain, and the type of the pain. The criteria used for radiating pain were: (a) any pain projected into the innervation pathway; and (b) any pain extending beyond the limits of the primary site.

2.4. Analysis

Logistic regression analysis was used to investigate the relationship between the response probability and the explanatory variables. Response was defined as complete or incomplete (i.e., partial or no response).

Analyses were performed for each variable separately and for the four groups of explanatory variables. A logistic regression model was constructed and its predictive capacity was evaluated.

Statistical analysis was performed using SAS/STAT version 6.07, SAS Institute Inc., Cary, NC, USA.

3. Results

A total of 75 patients met our inclusion criteria for the study. However, the physical condition of 24 participants deteriorated rapidly and they were unable to complete treatment. Therefore, the data on 51 patients could be analysed. Primary tumour site and patient characteristics are shown in Tables 1 and 2.

Before radiotherapy 33% of the patients had an NRS of 70 or more, 47% between 35 and 70, and 20% less or equal to 35. Four patients had neurogenic pain, 21 patients nociceptive pain and 26 a combination of neurogenic and nociceptive pain.

3.1. Response to radiotherapy

Complete response was observed in 12 (23.5%) patients (NRS = 0) and partial response in 18 (35.2%) patients and no response in 21 (42%). The pain score versus time for the two types of response is shown in Fig. 1. Complete response occurred within 21 days of the start of radiotherapy and the result was not due to any changes in the consumption of analgesics. Analgesic consumption remained stable for all patients.

Table 1

Primary site of malignancy and response to palliative radiotherapy

Site of primary tumour	No. of patients	
	Complete response	Partial/ no response
Primary unknown	1	1
ENT	1	2
Oesophagus	1	1
Colon	1	–
Rectum	–	1
Lung	–	6
Pleura	–	1
Lymphomas	1	3
Skin	1	–
Breast	4	11
Ovary	–	1
Prostate	2	6
Bladder	–	2
Kidney	–	3
Thyroid	–	1

3.2. Explanatory variables

No significant relationships were found between the response probability and any of the separate explanatory variables using logistic regression analysis ($P \geq 0.05$, likelihood ratio test). When the explanatory variables were analysed in groups, a significant relationship was found between the response probability and the pain characteristics: the presence of radiating pain and the pain score before radiotherapy ($P < 0.1$; Table 3). Using these two variables, the chance of achieving a complete response (p_c) can be calculated as:

$$Logit(p_c) = -2.3 + 2.2\ (radiating\ pain) - 1.6\ (pain\ num\ score)$$

where p_c is the probability of achieving a complete response. Patients with radiating pain and a pain score before radiotherapy of less than or equal to 35 had the

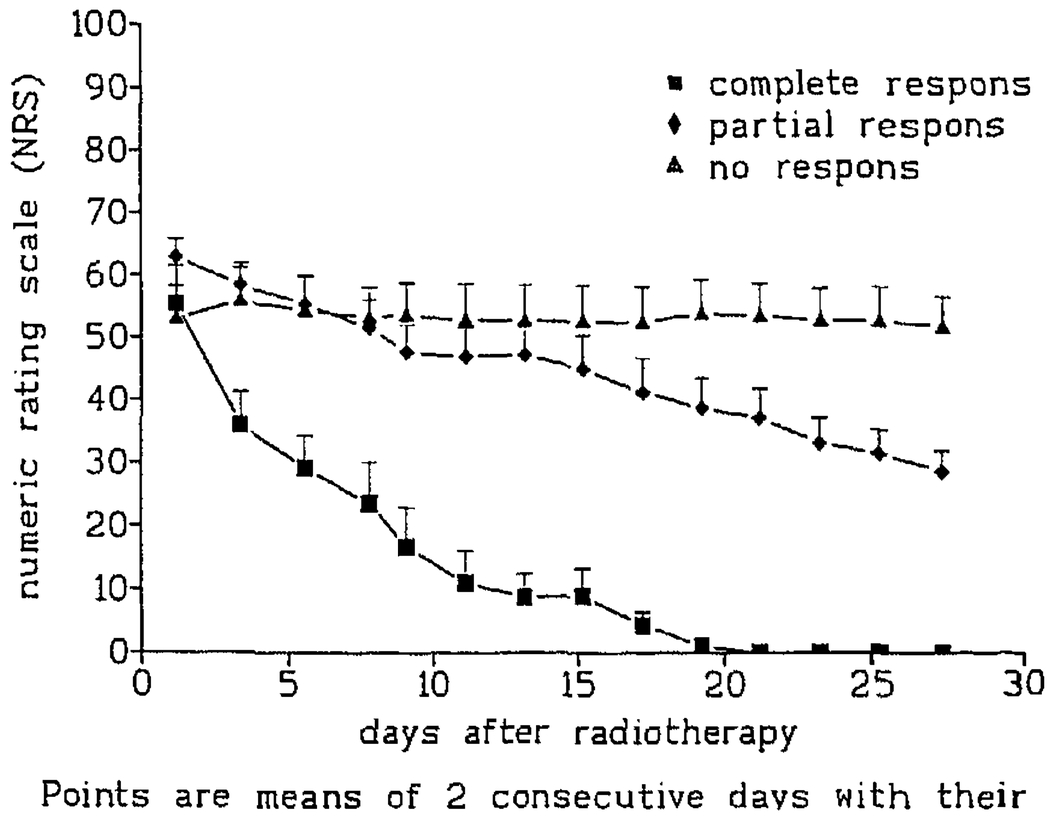

Fig. 1. Analgesic response after radiotherapy.

Table 2

Patient characteristics

	No. of patients		
	Complete response	Partial response	No response
Age (years, mean ± SD)	54 ± 11.5	56 ± 9.9	60 ± 11.7
Gender			
Male	8	11	10
Female	4	7	11
ECOG (0–4)			
0	9	9	17
>0 (1–3)	3	9	4
Co-therapy			
None/hormone	6	11	15
Chemotherapy	6	7	6
Metastases			
No	1	2	2
Yes	9	16	17
Radiotherapy, total dose			
1–8 Gy	2	6	2
9–29 Gy	10	4	16
≥30 Gy	0	8	3
Bone metastases			
No	1	4	0
Yes	11	13	19

Table 3

Dichotomy and P values of patients who showed a complete response ($n = 12$) versus partial or no response ($n = 39$)

Group	Explanatory variable	Dichotomy	P value inside the category
Patient	Age	<60, ≥60	0.32
	Gender	Male, female	
	ECOG	≥0.1	
Tumour	Gender × breast cancer	0.1	0.84
	Co-therapy	None/hormonal chemotherapy/ other	
	Metastases	No, yes	
	Bone metastases	No, yes	
Pain	Pain duration	≤12, 12	0.02
	Radiating pain	No, yes	
	Pain NRS	≤35, >35	
	Pain type	Nociceptive, neurogenic	
Radiotherapy	Total dose	≤8, >8	0.57
	Field size (cm^2)	≤165, >165	
	Treatment site	Spine, no spine	

best prognosis; 17 patients met these criteria and 8 of them showed a complete response. The overall correct classification was 75% (38/51).

4. Discussion

The majority of patients who participated in this study had a life expectancy of only a few months (Hoskin, 1988; Quilty et al., 1994) and the main objective of therapy was to provide pain relief while sparing them the extra burden of ineffective treatment. For the definition of a complete response to radiotherapy, it is necessary to apply strict criteria. In this study, we employed the following definition for a complete response: the patient had to become completely pain-free within 28 days after the start of treatment; this was achieved in less than 25% of the cases.

Four patients experienced a type of pain, which fulfilled the criteria of neurogenic: neuro-anatomically projected pain and signs of neural dysfunction. All the other patients had a nociceptive type of pain or a combination of both nociceptive and neurogenic. The radiating component of the pain was not considered to be an exclusive part of the neurogenic type of pain. Patients with a nociceptive pain could notify a radiating component that could be described as spreading according to nerve pathways or as extending beyond the limits of the primary site. It is often impossible to make a clear distinction between these two types of pain in cancer. No doubt this is due to the diffusely infiltrating growth pattern of neoplasms.

Of all the explanatory variables analysed, only the characteristics of pain itself (the presence of radiating pain and the pain score (NRS) before radiotherapy) proved to correlate with a complete response to radiotherapy.

In the literature, various non-randomised (prospective and retrospective) and randomised studies have described the efficacy of radiotherapy for providing cancer pain relief (Hoskin, 1988). Owing to different methods of pain assessment, possible changes in analgesic consumption during the evaluation period, heterogeneity of patient groups and radiotherapy techniques, it is not possible to draw conclusions about which radiotherapy technique is the best for relieving cancer pain and which variables are the most reliable predictors of efficacy.

Our study differed from the ones mentioned above on one specific aspect: we concentrated on exploring the value of explanatory variables which are related to pain. The study design was similar regarding other aspects, because patient selection was applied and we prescribed a pragmatic treatment technique.

The advanced stage of the primary disease in our patients and their poor general condition explained why 24 out of the 75 patients were unable to complete treatment. Similar drop-out rates have been reported in the studies by Price et al. (1986) and Tong et al. (1982). They found that using a self-assessment technique led to a decrease in compliance to less than 50% three months after treatment. In the study by Price et al., 30% of the patients died within three months of randomisation.

In our patient group, a complete response was observed in only 23.5%, which ranks among the lowest success rates reported in the literature. The use of strict criteria for the definition of a complete response (NRS = 0, within 28 days) and the pain assessment method may have been responsible for this outcome. Pain was assessed by the patient, not by a physician. In other studies in which pain was assessed by a physician, the response rates were higher, whereas in studies which employed self-assessment the apparent success rates of radiotherapy were lower (Hoskin, 1988).

In patients with a limited life expectancy, it is important for therapy to provide rapid pain relief. To avoid applying treatment which will be ineffective, explanatory variables are needed which can predict efficacy. In agreement with other authors, we found that the primary tumour characteristics and radiotherapy technique did not have any predictive value (Hoskin, 1991). The response rates were the same for tumour doses of ≤8 Gy and >8 Gy. An important finding in our study was that pain characteristics did have significant predictive value. The chance of achieving a complete response was highest in the patients with radiating pain and a low pain score before radiotherapy (NRS ≤ 35). These two pain characteristics have not been mentioned before as explanatory variables to predict efficacy and they may also indicate that radiotherapy has a fairly low analgesic effect.

In our animal experiments we found that irradiating the lumbar enlargement of the spinal cord with doses of 10, 15 and 17.5 Gy inhibited the behavioural response to pain stimuli (Rutten et al., 1994). We suggested that this anti-nociceptive effect was caused by destruction and exhaustion of the resources for neuro-transmission within the system which processes and transmits the pain signal.

An explanation of the usefulness of only radiating pain and low pain score and not any of the other pain characteristics as explanatory variables may be that different biochemical processes are responsible for the different pain characteristics. There were several analogies between the results of this study and those of our animal experiments. Firstly, the rats which were irradiated in our previous study did not have malignant tumours and it is known that tumour shrinkage is not an essential component of the initial analgesic response to radiotherapy. For example, rapid onset of pain relief has been observed after hypophysectomy, orchidectomy and half-body irradiation (Smith and Macaulay, 1985; Hoskin, 1988). Secondly, the effect in rats was evident in the hot-plate test but not in the tail-flick test, which indicates that the effect may be specific to certain pain characteristics. Therefore, it can be expected that pain characteristics will also be relevant explanatory variables in man. Thirdly, the maximum effect of irradiation in rats was a reduction in the behavioural response of approximately 50%. Thus, like in man,

the analgesic efficacy of radiotherapy was limited. In our opinion, to determine the exact mechanism of the analgesic effect of radiotherapy in man, attention should be focused on pain mechanisms rather than on the mechanisms involved in destroying tumour cells.

5. Conclusion

In this study on 51 patients, we found a significant relationship between pain characteristics (the presence of radiating pain and a low NRS score before treatment) and a complete response to palliative radiotherapy.

Future research should concentrate on the dynamic interactions between cancer, pain signal processing and irradiation to improve the reliability of explanatory variables for predicting the efficacy of palliative radiotherapy.

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