Original Paper

Quality of Life (QOL) Studies in Patients with Various Malignancies Treated with Local Hyperthermia Combined with Chemo-and/or Radiotherapy

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Abstract: Improvement in the quality of life (QOL) is considered to be one of the main goals in the treatment of patients with advanced cancer. The purpose of this study was to assess the QOL for patients during the course of combined treatments which included local hyperthermia (HT) plus chemotherapy and/or radiotherapy.

Eighty nine patients (M/F ratio was 44/45) with various malignancies were questioned using the Japanese version of the 'European Organization for Research and Treatment of Cancer (EORTC) QOL Questionnaire Core 30'. Assessment was performed before the beginning of HT therapy, and after 8 weekly sessions. In addition, a longitudinal study was performed with 14 patients after 16, 24 and 30 sessions.

It was seen that gender may influence various aspects of the QOL during the treatments. For instance, female patients performed better with regards to the social aspects whereas they displayed worse somatic parameters. Regarding age, although younger patients claimed more financial problems before HT, onset of HT did not cause any additional difficulties in this respect. Surprisingly, HT led to a better recovery from a loss of appetite in elderly patients. In considering the relationship between the QOL and treatment response, better responses were associated with both superior pretreatment emotional functioning and improvement in the QOL during the therapy. The best QOL performance was observed for patients with breast and lung cancer. In addition, patients who underwent long-term HT which lasted for 36 weeks, had stable QOL parameters throughout the entire period of observation. This leads us to suggest that somatic, social and psychological QOL parameters for cancer patients may be improved by combined treatment modalities which include HT. In addition, both pretreatment emotional status and improvement in the QOL during the course of treatment may influence the objective treatment outcome.

Key Words: somatic, social, psychological QOL, local hyperthermia

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Introduction

Advances in cancer therapy have led to improved objective outcomes such as survival, objective responses to treatment, and toxicity. Recently, key goals during the treatment of cancer have been, not only to achieve better survival times and responses, but also to produce an improvement in the patient's quality of life (QOL), and to maintain a good QOL during treatment. This is especially important for patients with advanced cancer who have limited survival expectancies[1,2]. Thus, evaluation of the QOL has been included as one of the major endpoints in many recent phase III trials for patients with advanced cancer[3].

Although no formal definition of a health-related QOL has yet been generally accepted, it has been agreed that this is a subjective, multidimensional concept comprising three major aspects of functioning : somatic, social, and psychological[4]. At a time when the advantage of a combination of local hyperthermia (HT) with conventional anticancer modalities in terms of both local control and survival has been demonstrated in several trials[5-8], QOL-related studies are still very limited since most of these studies have been designed to evaluate the possible negative impacts of the addition of local or regional HT with other treatment modalities[9-11].

The purpose of the present study was to determine the impact of combined treatments, with weekly local HT as the base therapy, on illness characteristics and psychopathological co-morbidity on the QOL of cancer patients. This was evaluated using the Japanese version of the 'European Organization for Research and Treatment of Cancer (EORTC) QOL Questionnaire Core 30' [12].

Patients and Methods

1) Patient characteristics

Patients with various malignancies who were treated with regional HT combined with chemo- or chemoradiotherapy were approached for this study. Their clinical characteristics are summarized in Table I.

Table I. Patients' clinical characteristics

Total (patients)	89	
M/F	44/45	
Age (yrs)	62.2±11.8	
	60 >	36
	60 ≤	53
Performance status (PS)	0	7
(Eastern Cooperative	1	62
Oncology Group)	2	18
	3	2
Tumor origin (n)	Lung	15
	Colon	15
	Breast	11
	Liver	9
	Pancreas	8
	Stomach	7
	Other	24
Tumors treated with HT (n)	Primary	5
	Recurrence	23
	Metastases	61
Treatment site (n)	Head and Neck	3
	Chest	28
	Abdomen	44
	Pelvis	14
Hyperthermia alone (HT)		7
HT+chemotherapy (C) (HCT)		77
R+C+HT (RCHT)		5

2) Heating

HT treatments were delivered by means of an 8 MHz capacitive heating device, the "Thermotron RF-8" (Yamamoto Vinita Co., Ltd., Osaka, Japan). Electromagnetic power ranging from 206 to 1500 W, depending on the treatment site, was applied between a pair of electrodes with diameters ranging from 7 to 30 cm (depending on the heating site) which were placed on the opposite sides of the target area. A saline solution maintained at 2-37°C was circulated in the boluses to avoid overheating of the skin. For premedication, 50 mg indomethacin (i.r.) was

administered 30 min before HT. A 1% xylocaine topical gel was applied to the skin to decrease the sensation of heat. Blood pressure and pulse were monitored during treatment. The time for one HT session was 40-60 min. HT was performed once a week.

3) QOL assessment

The QOL of individual patients was assessed by using the EORTC QLQ-C30 (version 3.0) questionnaire. This is a self-administered questionnaire, developed specifically for use in clinical cancer research.

As shown in Table II, the questionnaire contains 30 items grouped into 5 functional domains (physical, role, cognitive, emotional, and social), 3 symptom domains (fatigue, pain, nausea and vomiting), 5 single symptom items (dyspnea, insomnia, anorexia, diarrhea, and constipation), 1 item dealing with financial concerns, and a global health domain. The questionnaire employs 28 four-point response scales (not at all ; a little ; quite a bit ; very much), and 2 seven-point response scales for the global health and QOL domains. Patients indicate the extent to which they have experienced specific symptoms or functional limitations over the past week. In accordance with the EORTC QLQ-C30 scoring manual, all scores were linearly transformed into a numerical scale with values from 0-100. For items relating to symptoms, a higher score represents a higher level of symptoms. For scales related to function, a higher score represents a higher level of functioning. Assessment was performed before the onset of HT, and after 8, 16, 24 and 32 weekly HT sessions.

Table II. Scoring the QLQ-C30 version 3.0.

	Scale	Number of items	Item range*	Version 3.0 Item numbers
Global health status / QOL				
Global health status / QOL	QL	2	6	29, 30
Functional scales				
Physical functioning	PF	5	3	1 to 5
Role functioning	RF	2	3	6, 7
Emotional functioning	EF	4	3	21 to 24
Cognitive functioning	CF	2	3	20, 25
Social functioning	SF	2	3	26, 27
Symptom scales / items				
Fatigue	FA	3	3	10, 12, 18
Nausea and vomiting	NV	2	3	14, 15
Pain	PA	2	3	9, 19
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhoea	DI	1	3	17
Financial difficulties	FI	1	3	28

**Item range* is the difference between the possible maximum and the minimum response to individual items ; most items take values from 1 to 4, giving a *range*=3.

The data was evaluated using a paired t-test. p values < 0.05 were considered to be statistically significant.

3) Chemo-and radiotherapy

Before the onset of HT, most of the patients had already begun treatment using chemo- (C) and radiotherapy (RT) following protocols and doses appropriate to their tumor origins.

4) Evaluation of response

Local response was evaluated as follows: complete response (CR) when no tumor was detected by physical examination or computer tomography or/and magnetic resonance imaging; partial response (PR) when the tumor mass was reduced by $\geq 50\%$; no change (NC) when the reduction of the tumor mass was $< 50\%$; progressive disease (PD) when the tumor mass increased to over 20% of pretreatment levels.

Results

1. Treatment response

Among the 89 patients included in this study, 1 patient exhibited CR, 16 (18%) demonstrated PR, 41 (46%) exhibited NC, and 31 (35%) exhibited PD.

2. QOL and gender

As shown in Table III, there were no significant differences in QOL scores between male and female patients before treatment, except that female patients had a tendency to suffer more from insomnia and

Table III. QOL scores and gender.

Male/Female	Male		Female	
	Before	After	Before	After
global health status/QOL	55 (22)	61 (25)	52 (25)	60 (26)
physical functioning	81 (20)	78 (23)	76 (18)	73 (21)
role functioning	72 (24)	72 (26)	71 (32)	69 (33)
emotional functioning	80 (20)	83 (17)	78 (21)	77 (23)
cognitive functioning	77 (20)	77 (19)	79 (21)	79 (22)
social functioning	77 (23)	75 (25)	77 (30)	85 (23)
fatigue	34 (18)	35 (21)	33 (26)	39 (29)
nausea and vomiting	5 (11)	5[a] (9)	9 (19)	14[a](25)
pain	23 (24)	24 (26)	28 (31)	27 (30)
dyspnea	20 (23)	21 (19)	20 (56)	21 (25)
insomnia	20 (25)	19 (23)	29 (32)	21 (25)
appetite loss	22 (26)	29 (27)	20 (31)	23 (29)
constipation	24 (24)	26 (27)	30*(31)	23*(24)
diarrhoea	13 (24)	14 (24)	11 (24)	14 (23)
financial difficulties	20 (22)	22 (25)	31 (38)	22 (36)

All scores shown in this and other tables were linearly transformed into a 0-100 scale from the patient questionnaire responses. Scores are presented as means, and the numbers in the parentheses represent the SD.

[a]: $p < 0.05$

*: $p < 0.05$

constipation, and claimed more financial difficulties (Note that all scores shown in the tables were linearly transformed into a 0-100 scale from the patient questionnaire responses).

However, there was a difference in response to treatment between male and female patients, since female patients had better improvements in social functioning, and constipation, although they had a more difficult time dealing with nausea and vomiting.

3. QOL and age

It is of interest to note that before HT treatment there were no statistically significant age related differences, except that younger patients claimed more financial difficulties. The onset of HT did not cause any additional financial problems. After treatment, the only age-related difference found was that patients more than 60 years old showed better a recovery from loss of appetite than younger ones (Table IV).

Table IV. QOL scores and age.

Age	60 >		60 <	
	Before	After	Before	After
global health status/QOL	56 (23)	64 (25)	52 (23)	57 (26)
physical functioning	80 (15)	79 (18)	77 (22)	73 (24)
role functioning	74 (26)	71 (26)	70 (30)	70 (32)
emotional functioning	81 (18)	80 (20)	78 (22)	80 (21)
cognitive functioning	80 (18)	83 (18)	77 (22)	75 (22)
social functioning	78 (25)	81 (27)	76 (27)	79 (23)
fatigue	33 (19)	34 (22)	33 (24)	40 (27)
nausea and vomiting	7 (16)	5 (10)	7 (15)	12 (23)
pain	30 (32)	24 (25)	22 (24)	27 (30)
dyspnoea	14 (18)	19 (20)	24 (53)	23 (23)
insomnia	26 (33)	15 (20)	23 (27)	23 (27)
appetite loss	16 (26)	17*(20)	25 (29)	32*(31)
constipation	27 (25)	21 (21)	28 (30)	27 (28)
diarrhoea	9 (17)	13 (18)	14 (28)	15 (27)
financial difficulties	34**(39)	29 (38)	19**(22)	17 (24)

All scores shown were linearly transformed into a 0-100 scale from the patient questionnaire responses. Scores are presented as means, and the numbers in the parentheses represent the SD.

* $p < 0.01$

** $p < 0.05$

4. QOL and treatment response

Pretreatment emotional functioning was significantly better in patients who responded to treatment and those with stable disease when compared with non-responders (Table V). The rest of the items were comparable between responders, patients with stable disease, and those with progressive disease. Interestingly, there was no significant difference in emotional status among patients with performance status (PS) 0, 1, 2, however emotional status became significantly worse in patients with PS3. At the same time, PS itself was significantly better in responders (CR+RR group) when compared to

Table V. QOL scores and treatment response.

	CR+PR		NC		PD	
	Before	After	Before	After	Before	After
global health status/QOL	58 (21)	68 (23)	52*(22)	62*(25)	54 (25)	53 (28)
physical functioning	84 (16)	84 (16)	77 (18)	75 (19)	76 (23)	72 (28)
role functioning	70 (30)	77 (20)	71 (26)	71 (30)	73 (31)	65 (32)
emotional functioning	86[a](20)	87[c](20)	84[b](15)	85[d](18)	68[a,b](22)	70[c,d](20)
cognitive functioning	81 (15)	83 (16)	78 (20)	78 (20)	77 (24)	75 (24)
social functioning	72 (27)	82 (18)	82 (23)	84 (25)	72 (30)	73 (27)
fatigue	34 (21)	27[e](12)	31 (21)	33[f](26)	36 (24)	47[e,f](27)
nausea and vomiting	14 (24)	8 (13)	4 (11)	6 (17)	7 (14)	15 (24)
pain	36 (33)	18[g](19)	23 (24)	21[h](26)	24**(28)	36[g,h,**](32)
dyspnea	18 (17)	22 (20)	18 (24)	20 (20)	24 (66)	22 (26)
insomnia	24 (35)	6[j,k](13)	18[i](21)	17[j,l](20)	33[i](33)	31[k,l](31)
appetite loss	27 (34)	20[m](21)	18 (25)	20[n](24)	22***(29)	38[m,n,***](33)
constipation	24 (26)	24 (16)	26 (24)	27 (25)	31 (33)	23 (30)
diarrhoea	10 (20)	12 (20)	8 (21)	7 (15)	19 (29)	25 (30)
financial difficulties	25 (28)	14 (27)	25 (31)	19 (30)	26 (34)	30 (33)

All scores shown were linearly transformed into a 0-100 scale from the patient questionnaire responses. Scores are presented as means, and the numbers in the parentheses represent the SD.

*,** : $p < 0.05$*** : $p < 0.01$[f,g,h,i,j,l,m,n] : $p < 0.05$[a,c] : $p < 0.01$[b,d] : $p < 0.005$[e,k] : $p < 0.001$

non-responders (NC group) (data not shown).

During the course of treatment, global health status had a tendency to appear improved in responders. Furthermore, in patients with stable disease (NC group) this difference became statistically significant when compared with pretreatment levels. Responders also recovered significantly better from fatigue, had better pain control, and suffered less from insomnia and loss of appetite.

At the same time, there were no statistically significant group differences in the physical, role performance, cognitive and social functioning scores.

5. QOL and origin of malignancy

The QOL score was compared for six of the most common malignancies as shown in Table VI. For all groups, there was a treatment-related improvement of global health status to some extent, although it was statistically significant only for patients with breast cancer. It is of interest to note that in patients with breast cancer, the QOL was improved in as many as 12 of the 15 domains or items, although that improvement was statistically significant only for global health and role functioning. Similarly, lung cancer patients also demonstrated an improvement of their QOL under most of the criteria, however, these improvements did not reach statistically significant levels. The most disappointing results were for patients with pancreas and colon cancer who displayed impaired QOL scores for most of the criteria. Here, the extent of fatigue was significantly worse when compared to the other groups.

6. Longitudinal study of QOL

Patients who continued treatment for as long as 36 weeks have demonstrated stable QOL scores through the entire observation period (data not shown).

Table VI. QOL and origin of tumor.

	Lung		Colon		Breast		Liver		Pancreas		stomach	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
global health status/QOL	53 (16)	57 (24)	52 (25)	58 (26)	49*(27)	67*(24)	59 (20)	68 (32)	41 (30)	48 (20)	50 (26)	63 (38)
physical functioning	82 (20)	82 (16)	75 (26)	72 (26)	79 (14)	75 (16)	83 (14)	75 (23)	72 (19)	68 (26)	81 (16)	72 (35)
role functioning	72 (22)	79 (18)	63 (32)	67 (29)	61**(32)	79**(24)	81 (23)	78 (25)	65 (33)	54 (37)	79 (16)	74 (30)
emotional functioning	79 (18)	85 (18)	73 (28)	72 (25)	80 (20)	86 (23)	75 (20)	75 (19)	83 (13)	77 (21)	82 (20)	82 (16)
cognitive functioning	78 (20)	83 (19)	78 (29)	72 (26)	80 (15)	85[a](16)	83 (14)	87[b](16)	67 (20)	67[a,b](18)	81 (18)	76 (16)
social functioning	79 (19)	80 (19)	73 (33)	81 (14)	77 (33)	92 (14)	88 (17)	76 (32)	71 (32)	66 (35)	81 (24)	76 (25)
fatigue	32 (20)	29 (17)	37 (25)	46[c](30)	36 (25)	24[c,d](18)	29 (13)	35 (22)	43 (24)	47[d](24)	31 (20)	32 (31)
nausea and vomiting	2 (6)	3 (7)	12 (20)	16 (23)	14 (27)	3 (7)	2 (6)	6 (12)	2 (6)	5 (8)	19 (20)	5 (8)
pain	31 (29)	26 (27)	22 (27)	29 (33)	41 (38)	20 (15)	15 (14)	20 (23)	34 (37)	42 (37)	21 (19)	21 (37)
dyspnoea	38[e,f,g,h,i](25)	32[j,k](16)	13[e](21)	26[l] (28)	18[f](23)	18 (23)	7[g](15)	11[j](17)	8[h](15)	17 (25)	5[i] (13)	5[k,l](13)
insomnia	20 (21)	13 (17)	27 (29)	29 (31)	30 (38)	12 (23)	33 (33)	22 (29)	25 (24)	21 (25)	24 (37)	24 (37)
appetite loss	16 (25)	29 (25)	24 (34)	40 (31)	27 (39)	15 (23)	19 (24)	19 (24)	33 (31)	17 (18)	29 (30)	24 (37)
constipation	24 (27)	24 (28)	31 (32)	27 (26)	33 (30)	27 (25)	22 (33)	22 (33)	29 (33)	33 (25)	24 (16)	24 (25)
diarrhoea	11 (21)	10[p](16)	21[o](31)	33[p,q,r](31)	0[o] (0)	3[q](10)	11 (24)	11 (24)	4 (12)	8[r](24)	19 (38)	24 (32)
financial difficulties	27[s](29)	26 (33)	9[s](15)	11 (21)	33 (39)	24 (40)	21 (17)	33 (29)	37 (42)	37 (42)	29 (41)	19 (38)

All scores shown were linearly transformed into a 0-100 scale from the patient questionnaire responses. Scores are presented as means, and the numbers in the parentheses represent the SD.

*,** : $p < 0.05$, [a,b,c,d,f,l,m,n,o,p,r,s] : $p < 0.05$, [e,g,h,i,j,k,q] : $p < 0.01$

Discussion

Cancer occurrence itself has a negative impact on life[13,14]. Improvement in the QOL is an important goal in cancer treatment, and is a primary desire of patients, especially patients with advanced cancer, when symptom palliation is often the only option remaining. With a better understanding of the specificity of the QOL for various categories of patients, it may become possible to manipulate and design better treatment options.

Promising clinical results from the use of HT in the treatment of various malignancies makes it desirable to evaluate the influence of HT on different aspects of the QOL. It has been previously shown that HT did not lead to acceleration (as was observed with conventional therapy) in the deterioration of the QOL for prostate and rectal cancer patients[9,11] and might have positively influenced the QOL in ovarian cancer patients[10]. When these studies were designed, the objective was to determine the feasibility of HT instead of its potential to improve the QOL. Thus the results of this study cannot be directly compared to previous QOL studies.

An impact of gender on the QOL during cancer treatments has been previously shown for patients with rectal cancer treated with conventional therapy[15]. In the present study, it was found that when female patients were associated with worse physical performance (in agreement with Schmidt et al.), female patients still showed better improvements in social functioning.

Regarding age, although younger patients claimed more financial problems before HT, the onset of HT did not cause any additional difficulties in this respect. Surprisingly, HT led to better recovery of the loss of appetite in elder patients. Taking into account earlier reports stating that cancer patients aged over 70 years were more affected by impaired physical functioning, global health, and fatigue during

conventional therapy[16,17], it might be of clinical importance that the addition of HT not only did not cause further complications, but in contrast led to a better QOL in elderly patients.

Many authors have reported the possible influence of psychological factors on the QOL and fatigue[18]. Moreover, it was shown that psychological factors may predict treatment response and survival[19,20]. This data also shows that pretreatment emotional functioning was significantly better in patients responding to treatment and those with stable disease when compared to non-responders. In addition, global health status had a tendency to be improved in responders, and in patients with stable disease this difference became statistically significant when compared to pretreatment levels. Responders also recovered significantly better from fatigue, had better pain control, less suffering from insomnia and from loss of appetite. The best QOL performance was demonstrated for patients with breast[21] and lung cancer. Maintaining the QOL of patients during a long duration therapy, and after its completion is also one of the goals of cancer treatment[22,23]. In this study, patients who underwent long-term HT which lasted for 36 weeks, had stable QOL parameters throughout the entire period of observation.

Based on our observations, it is possible that the somatic, social and psychological QOL of cancer patients may be improved by combined treatment modalities. Patterns of change in the QOL during treatment can be influenced by several factors such as age and gender. Both pretreatment emotional status and improvement of QOL during the course of treatment may positively influence the objective treatment outcome. HT-based therapy can be used without negative impact on the QOL for a long treatment period.

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