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ORIGINAL ARTICLE

The role of loco-regional treatment in long-term quality of life in de novo stage IV breast cancer patients: protocol MF07-01Q

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Abstract

Background/objective Since more solid evidence has emerged supporting the effectiveness of loco-regional treatment (LRT), clinicians consider LRT a treatment option for selected de novo stage IV breast cancer (BC) patients. This is the first report on long-term quality of life (QoL) in a cohort of patients who were randomized to receive either LRT and then systemic treatment (ST) or ST alone in the protocol MF07-01. We aimed to evaluate QoL in patients living at least 3 years since randomization using scores from the SF-12 health survey.

Methods SF-12 (V2) forms were completed during visits of patients who were living 36 months after the randomization. We first calculated PCS-12 (Physical Health Composite Scale) and MCS-12 (Mental Health Composite Scale) scores from de novo stage IV BC patients and compared them with the scores of patients diagnosed with stage I–III BC who lived more than 3 years. Further, PCS-12 and MCS-12 scores were compared between the LRT and ST groups with de novo stage IV BC. Additionally, general health, physical functioning, role functioning, bodily pain, vitality, mental health, and social functioning were evaluated and compared between the groups. Considering age-related changes in QoL, we also compared PCS-12 and MCS-12 scores of patients below or above 55 and 65 years of age. Responses to four additional questions (compare your physical health, mental health, daily activities, and energy currently vs. at diagnosis of BC) were recorded, considering cultural differences.

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Results There were 81 patients in this analysis; 68% of patients ($n = 55$) had LRT, and 32% ($n = 26$) received ST. General health was good or very good in 62% ($n = 34$) in the LRT group and 66% ($n = 17$) in the ST-only group ($p = 0.63$). Mean PCS-12 score was 40.8 ± 1.6, and mean MCS-12 score was 43.4 ± 2.0 ($p = 0.34$ and $p = 0.54$, respectively). PCS-12 and MCS-12 score difference was lower than that of the general Turkish population (PCS-12 = 49.3 ± 12.8 and MCS-12 = 46.8 ± 13.0) and stage I–III BC patients (PCS-12 = 51.1 ± 0.5, MCS-12 = 45.7 ± 0.6). PCS-12 and MCS-12 scores were similar between the LRT and ST-only groups in patients younger and older than 55 and 65, but QoL scores were much better in stage I–III BC patients younger than 65 when compared to the scores of those with de novo stage IV BC. Although treatment with or without LRT did not affect physical health, mental health, daily activities, and energy at 3 years vs. at diagnosis of BC in de novo stage IV BC patients ($p > 0.05$), these variables were significantly better in stage I–III BC patients ($p < 0.001$).

Conclusion The current MF07-01Q study demonstrates that patient who had LRT has similar physical and mental health outcomes compared to ST only in a cohort of patients who lived longer than 3 years.

Trial registration

This study is registered on clinicaltrials.gov with identifier number NCT00557986.

Keywords Breast cancer · Stage IV · De novo · Surgery · Quality of life

Introduction

Breast cancer (BC) is the most common type of cancer and cause of cancer-related deaths in women. According to Globocan data, 2,088,849 new cases were reported worldwide in 2018 [1]. Although most BC cases are diagnosed at an early stage, up to 10% of patients have stage IV disease at the time of diagnosis; de novo stage IV BC constitutes 28% of patients with metastatic BC [2–4]. Notwithstanding stage IV disease being considered "incurable," studies have shown that certain patients, especially de novo stage IV BC patients, may have long-term survival [3–17]. Loco-regional treatment (LRT) is considered a disease management option for selected de novo stage IV BC patients, and studies, including metanalyses, show that LRT prolongs disease-free survival and overall survival [5–17]. Apart from retrospective studies, the MF07-01 trial is the first randomized study to show a statistically significant improvement in median survival with primary breast surgery compared to systemic treatment (ST) alone at 5-year follow-up evaluation in patients with de novo stage IV BC especially in the bone-only metastatic group [18].

In daily practice dealing with such a high burden of disease, prolongation of survival is the core objective, and other aspects of treatment, such as the quality of life (QoL), need to be addressed. BC treatment reduces patients' QoL regardless of their cultural, racial, and socioeconomical differences [19–21]. A study from the eastern Mediterranean region showed that only less than one third of BC patients had good QoL outcomes [19]. BC was reported as the most common cancer associated with depression in women [22]. Combined anxiety and depressive symptoms were detected in 44.5% of patients diagnosed with BC [23]. Many factors have an impact on QoL in BC patients; older age and long-term treatment and follow-up are considered risk factors for depression in this patient group [24]. Elderly cancer patients care more about health-related QoL than survival [24]. Although generally continuity of daily activities and ability to work are considered essential, pain is an important factor affecting QoL [25]. Unlike other types of cancer, patients with BC may experience impaired QoL due to arm-related disorders, loss of body image, and sexual problems [26].

While state of health, financial income, and social support are other factors contributing to QoL, the most important of all is the burden created by the treatment modality applied such as surgery, chemotherapy (CT), radiation treatment (RT), and hormonal modalities [26–35]. Since stage IV BC patients receive life-long ST, the effects of treatment modalities become more prominent. The impact of ST on QoL had been examined more thoroughly than the effect of surgery in this subgroup of BC patients [30–32, 34, 35]. Although the effect of surgery on QoL in BC patients has been examined in the literature, most of these studies do not include stage IV BC patients. The most frequent mastectomy and lumpectomy were compared, and studies showed that both surgical techniques have a similar effect on QoL. Some studies discuss that patient QoL is better with lumpectomy than with mastectomy since the cosmetic result after lumpectomy is better and the patient experiences less psychosocial trauma [36–38]. On the other hand, mastectomy patients are suggested to have better QoL due to patient perception that the cancer has been completely removed [39]. A study by Chow et al. reported that patients undergoing mastectomy have worse QoL than those undergoing lumpectomy in terms of physical, emotional, and functional well-being [29]. In the same study, when symptom burden was evaluated, it was more severe in the mastectomy group, but when the metastatic patients were excluded, no difference was observed between the two methods in terms of symptom burden. That was attributed to the fact that patients in the mastectomy group reported heavier symptom burden, as they had more metastatic disease [29]. In

another study evaluating the effect of mastectomy on QoL, women with mastectomy in the first postoperative year had better QoL than in the first postoperative month. In addition, the symptoms with the strongest effect on QoL were reported as ST side effects such as hair loss and fatigue [40]. Many studies have shown that the effect of mastectomy on body image results in worse emotional and physical QoL scores than lumpectomy [39, 41–44]. Thus, QoL might present as another challenge to consider about while choosing among different treatment options.

The results of the MF07-01 trial showing survival benefit of LRT in patients with de novo stage IV BC especially patients with isolated bone metastasis arises the question whether the advantage of surgery comes with a price of a lower QoL in those patients. Thus, in this study, we aimed to evaluate the QoL in patients who had LRT at least 3 years prior, using scores from the SF-12 health survey, in order to learn whether prolonged survival after LRT is accompanied with a decline of the QoL.

Materials and methods

The current study was planned to assess QoL in a cohort of patients randomized in the MF07–01 study. In the MF07-01 protocol, patients were randomly divided into two groups: the LRT and ST (LRT) group or the ST-only (ST) group. Patients in the LRT group received ST after surgery, and patients in the ST group were administered only ST after randomization. LRT treatment was planned as breast conserving surgery (BCS) or mastectomy according to its suitability to provide complete tumor resection, and axillary lymph node dissection (ALND) was performed for patients with clinical-positive axillary lymph nodes. Breast radiotherapy was also applied to patients who received BCS. The results of the MF07–01 study showed that the LRT + ST group demonstrated statistically significant improvement in median survival compared to ST alone; patients receiving LRT followed by ST had a 75% higher chance of living at least 5 years compared to patients who received ST-only [18]. The detailed protocol of study MF07-01 was previously published [18, 45].

Between November 2007 and December 2012, the MF07-01 study recruited 312 patients. Of these patients, 274 were eligible and were randomized into either the LRT ($n = 138$) or ST-only ($n = 136$) group. Among these patients, only 97 patients were alive after 36 months. There were 81 patients participating in this current study who completed the SF-12v2 form at their third year visit; 68% of patients ($n = 55$) had LRT, and 32% of patients ($n = 26$) received ST only. Sixteen patients declined to complete QoL the questionnares:7 were in the surgery group, and 9 were in the ST group.

The age distribution of the patient groups was similar, and the majority of the patients (86%) were younger than 65 years old ($n = 70$). Most of the patients had bone-only metastasis (55%), and there was no difference between the groups ($p = 0.83$). Sixty percent ($n = 33$) of patients had modified radical mastectomy, and 87% ($n = 48$) had ALND in the LRT group. Chemo- and hormone therapy, trastuzumab, and bisphosphonate usage and surgery/radiation therapy to the metastatic site were similar between the groups (Table 1).

The 12-item short-form version 2 (SF-12v2) was used to evaluate QoL in our study (http://orthotoolkit.com/sf-12). This is a multipurpose short form questionnaire derived from the 36-item short-form health survey [46]. SF-12 is a general-purpose, frequently used criterion that is not specific to a particular disease and provides a fast mental and physical health assessment. Questions on the SF-12 aimed to evaluate mental-physical functionality and overall health-related-QoL. PCS-12 (Physical Health Composite Scale) and MCS-12 (Mental Health Composite Scale) scores were calculated from the responses to 12 questions and ranged between 0 and 100 points; a zero score reflects the lowest QoL, while a score of 100 indicates the highest QoL [46]. Four additional questions (compare your physical health, mental health, daily activities, and energy currently vs. at diagnosis of BC) were asked, and responses were recorded

Table 1 Comparison of patient and treatment characteristics in de novo stage IV breast cancer patients who had loco-regional treatment with those who received systemic treatment only

	LRT[1] ($n = 55$), % (n)	ST[2] ($n = 26$), % (n)	p
Age (mean ± SE) years	51.3 ± 1.6	51.7 ± 2.2	0.90
BMI kg/m^2 (mean ± SE)	27.9 ± 0.9	28.3 ± 1.1	0.70
Radiation therapy to metastatic site	13 (7)	31 (8)	0.05
Surgery to metastatic site	7 (4)	12 (3)	0.52
Bone-only metastasis	56 (31)	54 (14)	0.83
Hormonotherapy	94 (52)	85 (22)	0.14
Chemotherapy	93 (51)	88 (23)	0.52
Bisphosphonates	29 (16)	23 (6)	0.57
Trastuzumab	20 (11)	23 (6)	0.75

[1] Loco-regional treatment

[2] Systemic treatment

Table 2 Comparison of patient and treatment characteristics between de novo stage IV breast cancer (BC) patients and stage I-III BC patients

	De novo stage IV BC ($N = 80$)	Stage I–III BC ($N = 201$)	p
Age (mean ± SE) years	51.4 ± 1.3	51.6 ± 0.8	0.86
BMI kg/m^2 (mean ± SE)	28.0 ± 0.7	25.1 ± 0.3	0.0002
Follow-up (months) (mean ± SE)	86.1 ± 2.3	76.2 ± 1.6	0.0005
Hormonotherapy % (n)	90 (72)	75 (151)	0.005
Chemotherapy % (n)	95 (76)	74 (148)	< 0.0001
Radiotherapy % (n)	42 (34)	88 (177)	< 0.0001

considering cultural differences. The SF-12v2 was completed by patients surviving at 36 months after randomization at the follow-up visit. Scores were compared between the two treatment groups (LRT group vs. ST-only group).

The PCS-12 and MCS-12 scores obtained in our study were also compared with PCS-12 and MCS-12 scores derived from patients diagnosed with stage I–III BC and who lived longer than 3 years. Those stage I–III BC patients were randomly collected from two breast surgeons' datasets and included 201 patients. The mean age was similar to that in the de novo stage IV BC patients (51.6 $\pm$ 0.8, $p = 0.98$), and the majority of the patients were younger than 65 years old (94%, $n = 189$). BCS was performed in 79% ($n = 158$), and ALND was done in 47% ($n = 95$) of the stage I–III BC patients in the comparison group. Most of the stage I–III BC patients (88%, $n = 177$) received RT, much more than in the de novo stage IV BC patients ($p = 0.0001$). In contrast, the frequency of patients receiving chemo- and hormone therapy was higher in the de novo stage IV BC patients than in the stage I–III BC patients ($p < 0.0001$) (Table 2).

Additionally, for comparison of our data to Turkish general population PCS-12 and MCS-12 scores, we used the single study that we could find, representing a healthy urban Turkish population [47]. Considering age-related changes in QoL, we further analyzed PCS-12 and MCS-12 scores by dichotomizing the study group according to age as patients below or above 55 and 65 years of age.

The centers participating in the study received ethics committee approval prior to the start of the study.

Statistical analysis

Distribution of categorical variables among the groups was analyzed using chi-square tests. Continuous variable differences between the two groups were analyzed using the t test, and differences between three groups were tested with ANOVA followed by pair-wise t tests with multiple test corrections to identify groups statistically different from each other. Statistical analyses were conducted with the R program version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria, https://www.r-project.org).

Results

The results of our study showed that based on the SF-12 (V2), the mean PCS-12 score was 41.4 ± 1.3, and the mean MCS-12 score was 44.6 ± 1.0 in de novo stage IV BC patients. PCS-12 and MCS-12 scores were lower than in the general Turkish population (PCS-12 = 49.3 $\pm$ 0.1, and MCS-12 = 46.8 $\pm$ 0.1; Table 3). Stage I–III BC group PCS-12 and MCS-12 scores were 50.9 ± 0.6 and 45.7 ± 0.6, respectively; PCS-12 was statistically higher in the stage I–III BC patients compared with de novo stage IV BC patients ($p < 0.001$), but MCS-12 scores were similar (Tables 3 and 4; $p = 0.49$).

Comparison of LRT vs ST groups showed that general health was good or very good in 62% ($n = 34$) in the LRT group and 66% ($n = 17$) in the ST-only group ($p = 0.63$). There was no difference between the LRT and ST-only groups regarding PCS-12 and MCS-12 scores ($p = 0.34$ and 0.54, respectively) (Table 3). Twenty-eight patients (51%) in the LRT group and 10 patients (38%) in the ST-only group reported below-average PCS-12 scores ($p = 0.29$). For MCS-12, 18 patients (33%) in the LRT group and six patients (23%) in the ST-only group reported below-average scores ($p = 0.37$). Eighty-six percent of patients ($n = 70$) were younger than 65, and PCS-12 and MCS-12 scores were similar in the LRT and ST-only groups in patients younger and older than 65. PCS-12 scores were statistically higher in stage I–III patients compared with de novo stage IV BC patients ($p < 0.001$), but MCS-12 scores were similar ($p = 0.40$) in patients younger than 65 years old (Table 3). The mean PCS-12 and MCS-12 scores were similar in stage I–III BC patients compared with LRT and ST-only patients older than 65 years old ($p = 0.18$, and $p = 0.39$, respectively). Regarding the age cutoff of 55, PCS-12 and MCS-12 scores were similar between the LRT and ST-only groups ($p < 0.05$); however, PCS-12 scores were better in stage I–III patients compared with LRT and ST-only patients ($p < 0.001$).

Comparing physical health, mental health, daily activities, social interaction, and energy currently vs. at diagnosis of BC, all were found similar between the LRT and ST-only groups in stage IV BC ($p > 0.05$) (Table 3). However, the PCS-12 score and physical health, mental health, daily activities, social interaction, and energy currently vs. at diagnosis of BC were

Table 3 Comparison of PCS-12 scores and MCS–12 scores and physical and mental health, daily activities, and energy level currently vs. at diagnosis of breast cancer (BC) in patients who lived ≥ 3 years between the groups

	LRT[1] ($n = 55$)	ST only[2] ($n = 26$)	Stage I–III BC ($n = 201$)	p[3]	General population
[a]PCS-12 score mean ± SE	40.8 ± 1.6	43.4 + 2.0	51.1 ± 0.5	< 0.0001	49.3 ± 0.1
[b]MCS-12 score mean ± SE	44.2 ± 1.3	45.6 ± 1.6	45.7 ± 0.6	0.49	46.8 ± 0.1
[c]Age < 55					
PCS-12 score mean ± SE	43.3 ± 1.7	44.4 ± 1.8	50.8 ± 0.5	< 0.0001	
MCS-12 score mean ± SE	43.2 ± 1.3	47.0 ± 1.3	46.4 ± 0.6	0.11	
[d]Age ≥ 55					
PCS-12 score mean ± SE	36.3 ± 1.4	42.2 ± 2.1	52.0 ± 0.6	< 0.0001	
MCS-12 score mean ± SE	46.0 ± 1.3	43.8 ± 1.8	43.7 ± 0.6	0.61	
[e]Age < 65					
PCS-12 score mean ± SE	40.9 ± 1.4	43.9 ± 2.0	51.3 ± 0.5	< 0.0001	
MCS-12 score mean ± SE	44.2 ± 1.3	44.9 ± 1.5	46.0 ± 0.5	0.40	
[f]Age ≥ 65					
PCS-12 score mean ± SE	39.9 ± 1.4	38.9 ± 2.5	47.6 ± 0.7	0.18	
MCS-12 score mean ± SE	43.9 ± 1.5	50.9 ± 1.6	41.7 ± 0.7	0.39	
	LRT[1] ($n = 55$)	ST[2] ($n = 26$)		p	
	% (n)	% (n)			
Current physical health vs. at diagnosis of breast cancer	Same = 49% (27)	Same = 50% (13)		0.27	
	Better = 11% (6)	Better = 23% (6)			
	Worse = 40% (22)	Worse = 27% (7)			
Current mental health vs. at diagnosis of breast cancer	Same = 55% (30)	Same = 42% (11)		0.49	
	Better = 20% (11)	Better = 31% (8)			
	Worse = 25% (14)	Worse = 27% (7)			
Current daily activities vs. at diagnosis of breast cancer	Same = 18% (10)	Same = 23% (6)		0.75	
	Better = 47% (26)	Better = 50% (13)			
	Worse = 35% (19)	Worse = 27% (7)			
Current energy vs. at diagnosis of breast cancer	Yes = 45% (25)	Yes = 50% (13)		0.70	
	No = 55% (30)	No = 50% (13)			

[1] Loco-regional treatment in de novo stage IV BC

[2] Systemic treatment in de novo stage IV BC

[3] p value of comparison between LRT, ST, and stage I–III BC groups

[a] Comparison of PCS-12 scores between the LRT and ST groups, $p = 0.34$

[b] Comparison of MCS-12 scores between the LRT and ST groups; $p = 0.54$

[c,d,e,f] Differences between PCS-12 and MCS-12 scores in the LRT and ST groups are not statistically significant ($p > 0.05$)

Table 4 Comparison of PCS-12 scores and MCS-12 scores and physical, mental health, daily activities, and energy level currently vs. at diagnosis of breast cancer (BC) between de novo stage IV BC patients and stage I–III patients

	De novo stage IV BC, % ($n = 81$)	Stage I–III BC, % ($n = 201$)	p
PCS-12 score, mean ± SE	41.4 ± 1.3	50.9 ± 0.6	< 0.0001
MCS-12 score, mean ± SE	44.6 ± 1.0	45. 7 ± 0.6	0.36
Current physical health vs. at diagnosis of BC	Same = 50 (40) Better = 15 (12) Worse = 35 (28)	Same = 37 (75) Better = 59 (118) Worse = 4 (8)	< 0.0001
Current mental health vs. at diagnosis of breast cancer	Same = 50 (40) Better =19 (24) Worse = 26 (21)	Same = 37 (74) Better = 57 (114) Worse = 6 (13)	< 0.0001
Current daily activities vs. at diagnosis of breast cancer	Same = 20 (16) Better = 49 (39) Worse = 31 (25)	Same = 45 (91) Better = 48 (96) Worse = 7 (14)	< 0.0001
Current daily social interactions with family, friends, and relatives vs. at diagnosis of breast cancer	Same = 71 (57) Better = 15 (12) Worse = 14 (11)	Same = 39 (78) Better = 58 (116) Worse =3 (7)	< 0.0001
Currently more energy vs. at diagnosis of breast cancer	Yes = 46 (37) No = 54 (43)	Yes = 90 (181) No = 10 (20)	< 0.0001

statistically significantly better in stage I–III BC patients compared with de novo stage IV BC patients (Table 4; $p < 0.0001$).

Discussion

Since the long-term survival advantage of LRT, especially in the bone-only group, was shown in the randomized MF07-01 study, we compared the effect of LRT vs. ST only on QoL in patients with de novo stage IV BC as a secondary outcome of the MF07-01 study. This study shows that there was no difference in terms of QoL scores between patients in the LRT and ST-only groups who were surveyed at least 36 months after randomization. Currently, there are no studies in the literature evaluating long-term QoL in de novo stage IV BC patients who have undergone primary tumor surgery. QoL scores of BC survivors are worse in early treatment periods when STs are intense [29–32, 48]. In fact, in a Chinese study where patients received six cycles of CT for BC, the fourth and fifth cycles of CT reported to show the most negative effect on QoL [49]. In another study evaluating QoL and symptom burden, patients with metastatic BC were found to have more symptom burden and lower QoL. Especially in patients with early BC, more symptom burden and lower QoL scores were found in patients receiving CT. In addition, depression is more common in those who use selective estrogen receptor modulators (SERMs), and QoL is worse than for those who do not receive SERMs [30]. In our study, QoL scores were similarly low in both treatment arms, as CT and hormone therapy were the mainstay of treatment (91% of patients were taking hormone therapy and a similar number of patients had CT). However, it is notable that in de novo stage IV BC patients, adding surgery to ST does not worsen physical QoL already lower than that of the general population. Considering the survival advantage observed at 5 years in the LRT group, we may conclude that LRT provides a survival benefit without affecting QoL in these patients.

Apart from the factors mentioned above, other factors may also influence QoL. These include emotional factors such as anxiety and depression, as well as financial factors such as employment, and long-term effects related to treatment, which can be improved by the intervention [23, 27, 50]. Even though these factors were not recorded on in our study, we may expect similar effects on QoL independent of LRT in patients with stage IV disease receiving intensive ST. On the other hand, arm symptoms (such as lymphedema, pain, and motion limitation) are considered an additional factor that may influence QoL with surgical treatment. In our study, although ALND was applied in all patients in the LRT group, there was no difference between physical QoL scores of the group receiving LRT and those of the group receiving ST only. As a result, we think that surgical complications associated with LRT constitute an acceptable risk while considering the survival advantage it confers.

In our study, we found that patients with BC had lower QoL scores than the general population, regardless of whether or not primary tumor surgery was performed. In a study involving 1513 patients, Hamer et al. reported that patients with metastatic BC had the worst QoL scores and symptom burden among all stages of BC [30]. Although overall emotional stress and body image are important factors among those affecting QoL in BC patients, factors such as fatigue and pain due to metastatic disease and side effects of life-long ST are more dominant in metastatic BC patients. Considering the

physical and emotional effects of cancer on a patient, it is predictable that stage IV cancer will cause the worst effect.

The literature suggests that QoL is worse in younger BC patients [30, 48, 51]. It was found that the decrease in QoL was more prominent in those younger than 50 years old than those older. In addition, patient QoL in the first 2- to 10-year period after treatment was shown to be lower than those who completed 10 posttreatment years [30]. In our study, no difference was observed in QoL scores of either patients older or younger than 55 who had primary breast surgery or received ST only and lived more than 3 years. That discordance with the literature can be explained by the fact that patients examined in the studies have early-stage BC, and factors such as sexual functioning and body image, which may have a more important effect on QoL in the early stages, are less prominent in patients with metastatic BC. Similarly, in our study, the PCS-12 score was better in the stage I–III BC patients compared with de novo stage IV BC patients ($P < 0.001$); in the patients who survived more than 3 years, daily activities, social interactions, and having more energy were statistically significantly better in stage I–III BC patients compared with de novo stage IV BC patients ($p < 0.0001$). These worse scores can be attributed to life-long ST and metastatic BC patients frequently receiving metastatic workups such as positron emission tomography/computed tomography scans. In contrast, most of the time stage I–III BC patients receive limited CT and regular cancer follow-up images.

Our study had a few limitations. First, the number of patients in the study was low. Studies with more patients would determine the generality of our results. Second, we were not able to assess change in QoL over time. Third, a more detailed analysis using additional QoL assessment methods is necessary.

Conclusion

The randomized MF07–01 study showed that LRT prolongs overall survival in patients with de novo stage IV BC especially in the bone-only metastatic group. The current MF07–01Q study demonstrates that patient who had LRT has similar physical and mental health outcomes compared to ST only in a cohort of patients who lived longer than three years.

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